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Original Research Article

A novel approach in non-surgical management of tubal ectopic: combination of minimally invasive technique under ultrasound guidance with systemic methotrexate based on initial beta-HCG levels

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ABSTRACT

Background: Single dose methotrexate is the most preferred method of non-surgical management of unruptured tubal ectopic. A 2-dose regimen is suggested to treat tubal ectopic with higher trophoblastic cell load. Minimally invasive technique of ultrasound guided intracardiac KCL instillation along with systemic methotrexate has been in use even for live ectopic pregnancy. Objective of the study was to evaluate the success rate of single dose regimen of MTX (Methotrexate), 2-dose regimen of MTX and ultrasound guided instillation of intracardiac KCl in three different cohort of unruptured tubal ectopic pregnancy with an attempt to increase success of non-surgical management.
Methods: Fifty-eight women with unruptured tubal ectopic pregnancy were assigned to treatment protocols according to the initial β-HCG levels and presence/absence of FCA (fetal cardiac activity). Group 1: presence of FCA in the tubal ectopic; Group 2: initial β-HCG ≤5000 IU/ml; Group 3: initial β-HCG ≥5000 IU/ml without FCA. Women in group 1 were treated with ultrasound guided instillation of intracardiac KCl combined with systemic MTX. While women in group 2 were administered single dose regimen of MTX and group 3 received 2-dose regimen of MTX.
Results: Overall success rate of non-surgical management was 89.3% across all groups. Success rate in Group 1 was 78.6%. Success rate was 93.1% in group 2 while 92.3% in group 3. Rupture rate was 1.7% in the present study.
Conclusions: For non-surgical management categorizing and treating is an option with good result. Women with presence of cardiac activity can opt for non-surgical option with likely resolution in 78% cases.

Keywords: Ectopic, Methotrexate, Potassium Chloride, Pregnancy, Tubal, Ultrasound

INTRODUCTION

Non-surgical management for unruptured tubal ectopic pregnancy has become an established mode of treatment.[1,2] Overall success rate of MTX therapy ranges from 71-94%.[3,4] It is an attractive option as it reduces morbidity, hospital stay and averts surgical complications at potentially lower costs.[5,6] It also preserves the future fertility and ovarian reserve.[7,8]

Non-surgical management of unruptured tubal ectopic was traditionally done with fixed multiple dose regimen of MTX similar to the regimen used for gestational trophoblastic disease.[9] To minimize the side effects and increase compliance a single dose regimen was proposed by Stovall et al.[10] Single dose regimen has lesser adverse effects, is less expensive, requires less intensive monitoring and does not require folinic acid rescue. Single dose regimen is a misnomer because additional doses of MTX are sometimes required in poor responders.

With the aim of developing an optimum regimen that balances the efficacy and safety on one hand and convenience on the other a 2-dose MTX regimen (50

mg/m^2 intramuscularly (IM) on days 0 and 4) was proposed by Barnhart et al.[11] Success rate with this regimen was 87%.[11] This regimen had infrequent complications, less adverse effects and high patient satisfaction. It also has the advantage of close proximity of the second to the first dose which enhances the drug's effect on women with a high trophoblastic cell load.[12] This study yielded better success rate than single dose protocol with moderately high initial β-HCG levels and larger ectopic mass diameter.[11] Recent randomised control trials on single dose versus 2-dose validates the fact that 2-dose regimen has a higher success rate when initial β-HCG>5000 miu/ml.[29,30]

Ultrasound (US) guided intracardiac injection of potassium chloride (KCL) or methotrexate (MTX) has evolved as a new minimally invasive technique to treat women with advanced ectopic pregnancy who are less likely to respond to systemic MTX alone.[13-19] Wang et al reported a success rate of 93.3% in women who were treated with combined US guided intracardiac KCL or MTX than with only systemic MTX (73%), ($p<0.05$).[14]

Live ectopic pregnancy can also be treated with minimally invasive technique combined with systemic MTX. Non-surgical management is a pragmatic, formalised and novel approach of treating tubal ectopic pregnancy where an attempt has been made to incorporate the advantages of both local and systemic therapies. It includes US guided intracardiac KCL wherever feasible combined with systemic MTX. Dosing of systemic MTX also vary according to initial β-HCG levels (Figure 1). It is an approach to manage different types of tubal pregnancy with different regimens so that the scope of non-surgical management can be safely widened.

The present study was performed to compare the non-surgical management in women with tubal ectopic pregnancy with different initial β-HCG levels and even with some presenting with FCA. However, this study is not a comparative analysis of three different modalities of non-surgical management but with an intention to wider the accessibility and acceptability of the same as shown in the Figure 1.

METHODS

A prospective longitudinal study was conducted at Post Graduate Institute of Medical Education and Research, Chandigarh between June 2015 to September 2016. Approval for the study was obtained from the institutional ethics committee.

All women who desired non-surgical management were recruited. The inclusion criteria were (1) Presence of unruptured tubal ectopic pregnancy with or without fetal cardiac activity, (2) hemodynamic stability and (3) No or mild abdominal pain, (4) no contraindication to methotrexate therapy, (5) willing for follow-up.

The diagnosis of ectopic pregnancy was made when the β-HCG level was in the discriminatory zone of more than 1500 miu/ml with ultrasound evidence of extra uterine gestational sac or heterogeneous mass separate from ovary with or without evidence of fetal cardiac activity.

Non-surgical management protocol

Baseline investigations in the form of CBC, renal and liver function tests were done apart from serum β-HCG at the beginning of the non-surgical treatment. All the women in the study were informed about possible side effects of MTX, possibility of tubal rupture and intra-abdominal haemorrhage necessitating surgical intervention, protocol for serum β-HCG monitoring, possibility of needing additional doses of MTX and possibility of failure of non-surgical management. Written informed consent was obtained from all the cases in the study.

Women eligible for non-surgical management of ectopic pregnancy were categorised into 3 groups as shown in the Figure 1.

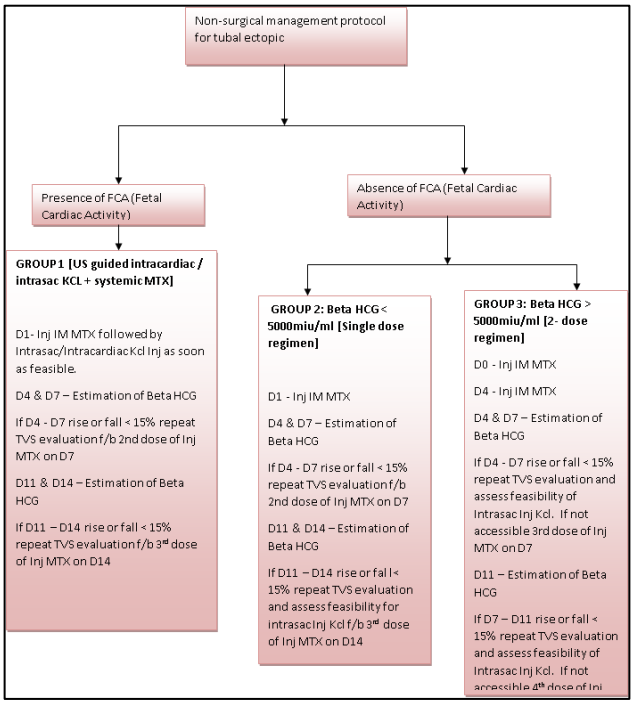

Figure 1: Management protocol.

Group 1-Women with presence of live ectopic pregnancy, group 2-Women with β-HCG ≤5000 miu/ml without fetal cardiac activity and group 3-Women with β-HCG ≥5000 miu/ml without fetal cardiac activity.

In group 1 women with live ectopic pregnancy the level of β-HCG was recorded and based on the calculation of body surface area a dose equivalent to 50 mg/m^2 was given and subsequently a TVS guided intracardiac KCl (2-3 meq) was administered using a 20 cm long 20-gauge needle using needle guide attached to the vaginal probe. The

procedure was considered complete after the disappearance of FCA. Subsequently β-HCG was measured on day 4 and day 7.

Women categorised under group 2 (β-HCG ≤5000 miu/ml) were treated with single dose regimen of MTX on day 1 and β-HCG was assessed on day 4 and day 7. If adequate fall (more than 15%) was recorded between day 4 and day 7 then treatment was considered successful. In women with no response, increase of β-HCG a 2nd dose of MTX was given on day 7. No women were given more than 3 doses of MTX (Figure 1).

Women categorised under group 3 (β-HCG ≥5000 miu/ml) were treated with 2-dose regimen of MTX. 1st dose of MTX was administered on day 0 [propounded by Barnhart et al as the day of 1st dose of MTX] and 2nd dose on day 4.[11] Estimation of β-HCG was done on day 4 and day 7. If there was rise or fall of β-HCG <15%, 3rd dose of Inj MTX was given on day 7. No women were given more than 3 doses of MTX (Figure 1).

Successful response to non-surgical therapy was defined as the decline in serum HCG levels to ≤15 mIU/ml with one or more doses of MTX or combined MTX with US guided intracardiac KCL and without the need for surgery.

Failure was defined if β-HCG did not decline with the treatment as per her protocol and/or patient required laparotomy/laparoscopy any time during treatment or follow up.

Statistical analysis

Discrete categorical data were represented in the form of either a number or a percentage. The normality of quantitative data was checked by measures of Kolmogorov-Smirnov tests of normality. Proportions were compared using Chi square or Fisher's exact test. For normally distributed data means of different parameters for 3 groups of β-HCG levels were compared using one-way ANOVA followed by post Hoc multiple comparisons test. For skewed data Kruk Sal-Wallis test followed by Mann-Whitney test for two groups was applied. For normally distributed data Student t-test was applied to compare 2 groups (successful group and unsuccessful group). For comparison of 2 groups of skewed data Mann-Whitney U test was used. To find independent predictors of success; logistic regression analysis was applied.

All the statistical tests were two-sided and were performed at a significance level of α=0.05. Analysis was conducted using IBM SPSS statistics (version 22.0).

RESULTS

A total of 128 women were diagnosed with tubal ectopic pregnancy. Seventy (54.68%) women presented with acute symptoms and were diagnosed as ruptured tubal ectopic. They were referred for surgery. Fifty-eight (45.31%) were haemodynamic ally stable with unruptured tubal ectopic pregnancy and were eligible for non-surgical management (Figure 2).

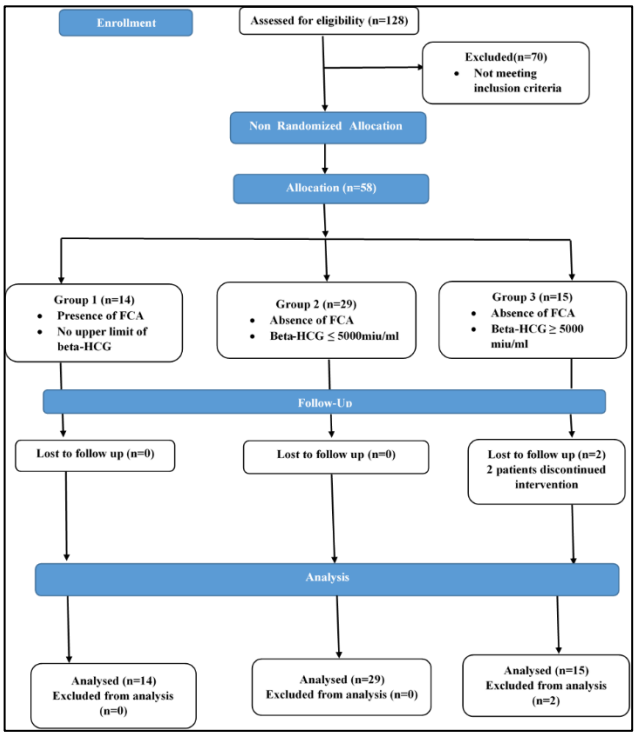

Figure 2: Flow of patients.

These 58 women assigned according to the initial β-HCG level values and presence or absence of FCA to a treatment according to the protocol of non-surgical management (Figure 1). Demographic characteristics have been shown in Table 1.

Mean period of gestation at admission calculated from last menstrual period was 6.8 weeks. Size of tubal mass is defined by measuring the biggest diameter of the tube with gestation seen on TVS.[20,21] In women where gestational sac, yolk sac or crown rump length could be visualised, size of the tubal mass was determined by taking the biggest linear diameter of gestation seen at TVS. While in women where a heterogeneous mass was observed at TVS, largest linear diameter of ectopic mass was taken as the size of the tubal mass. Overall mean size was 2.1cm (SD±1.2) with minimum size of 0.4 cm and maximum size of 6.4 cm (Table 1).

Mean β-HCG level in group 1 [live ectopic pregnancy] was 15,547.45 miu/ml (SD±7691.1). In group 2 [initial β HCG ≤5000 miu/ml] mean β-HCG level was 2689.7 miu/ml (SD±941.9) while in group 3 [initial β-HCG ≥5000 miu/ml] it was 9013.6 miu/ml (SD±4596.7). Initial β-HCG level was higher in group 1 as expected. Maximum number of doses of MTX administered per women was 3. All women irrespective of groups received 1st dose of systemic MTX.

Table 1: Baseline characteristics of the study cohort across 3 groups.

Characteristics	Group 1 (presence of FCA), n=14	Group2 (beta-HCG<5000 mIU/ml), n=29	Group 3 (beta-HCG>5000 mIU/ml), n=15	P value
Age, mean(±SD) (Years)	30±3.28	28.93±4.45	29.90±4.08	0.10
Gravidity, mean(±SD)	2.71±1.49	2.62±1.44	2.60±1.40	0.97
Parity, mean(±SD)	0.64±0.92	0.65±0.81	0.86±0.99	0.14
p/h/o infertility (%)	14.2	17.1	26.7	
p/h/o ectopic (%)	21.4	17.2	0	0.18
Period of gestation, mean(±SD) (Weeks)	6.96±1.04	6.40±1.14	7.73±1.61	0.006
Tubal mass, mean(±SD) (cm)	1.97±1.21	2.24±1.36	2.03±1.23	0.683
Resolution time of beta-HCG, mean(±SD) (Days)	35.28±20.70	32.37±10.02	35.40±20.49	0.10
Initial beta-HCG level, mean(±SD) (mIU/ml)	15547.45±76, 91.18	2689.79±941.96	9013.68±4596.76	<0.001
Success rate (%)	78.6	93.1	92.3	0.32

One patient in group 3 opted out of non-surgical management after receiving the first dose of MTX while another patient in group 3 did not receive the 2nd dose of MTX due to protocol deviation during initial phase of this study.

As women in group 3 [β-HCG ≥5000 miu/ml] were assigned to 2-dose regimen significantly higher percentage of women (86.7%) received 2 doses of MTX (p<0.001), while 13.3% of women in this group received the 3rd dose. Interestingly, women in group 1 [live ectopic pregnancy] whose mean initial β-HCG levels was significantly higher than group 2 [initial β-HCG ≤5000 miu/ml] and group 3 [initial β-HCG ≥5000 miu/ml] did not require 3rd dose of MTX. Half of the women in group 1 received 2nd dose of MTX while none received the 3rd dose. In group 2, 14% of women received the 2nd dose while 3.4% of women received the 3rd dose of MTX. No women received 4 doses of MTX.

Mean time required for initial serum β-HCG to decline to <15 miu/ml was 35.28 days, 32.37 days and 35.40 days in group 1, group 2 and group 3 respectively (Table 1). Time taken for resolution was not different among three groups.

Relation of initial β-HCG levels, total number of doses of systemic MTX and time taken for resolution of ectopic pregnancy was further analysed by Pearson correlation method. It was observed that if initial β - HCG levels were higher than it took longer for β-HCG levels to come back to normal (r=0.702, p=0.000) and higher number of doses of MTX were required for treatment. (r=0.285, p=0.030)

Success rate of the non-surgical management protocol was analysed with an intention to treat basis. It was observed that although the success rate (78.6%) was lowest in group 1 with all women having live ectopic pregnancies it was not significantly different from the other 2 groups. The overall success rate of non-surgical management was 86.21%.

Overall success rate after analysing these 56 women was 89.3%. Success rate was 78.6% in group 1, 93.1% in group 2 and 92.3% in group 3 respectively.

Statistical significance was not observed on applying Fisher exact test when group 1 vs. group 2 (p=0.371), group 1 vs. group 3 (p=0.653) and group 2 vs. group 3 (p=0.999) was compared.

Nominal regression analysis was done between success of non-surgical management and range of initial β-HCG levels in the study cohort. It revealed success with treatment declines with increasing β-HCG levels.

Risk estimate was analysed in the cohort by comparing initial β-HCG ranges. Although increasing β-HCG ranges had more probability of failure but statistical significance was not observed (Table 2).

Table 2: Risk estimate according to initial β-HCG ranges.

Beta-HCG ranges (mIU/ml)	Odds ratio (95% confidence interval)	P value
1500-2999 vs 3000-4999	0.500 (0.028, 8.952)	1.00
3000-4999 vs 5000-9999	0.611 (0.047, 7.882)	1.00
5000-9999 vs 10,000-14,999	0.846 (0.671, 1.067)	0.575
10,000-14,999 vs ≥15,000	1.286 (0.907, 1.823)	0.505

Initial β-HCG level was compared with success of Non-surgical management of ectopic pregnancy. The ROC

curve constructed in this study failed to provide any cut-off value of β-HCG level beyond which non-surgical management would be contraindicated (Figure 3).

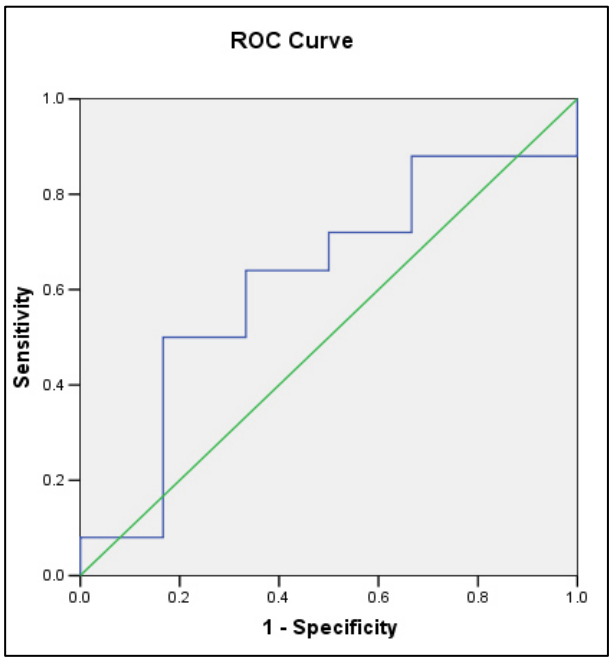

Figure 3: ROC curve.

Multivariate analysis was performed to observe the predictors of success or failure in this study. The predictors which were studied were pre-treatment β-HCG, D1 β-HCG, FCA, pain, free fluid in pelvis, tubal mass size, presence of gestational sac and yolk sac.[31,32] The predictors were compared with the outcome of Non-surgical management. However, these predictors failed to be of any significance in this study.

Six women resorted to surgery due to failure of non-surgical management. Intraoperative findings revealed that five women had tubal abortion while only one had rupture. Rupture rate in the study cohort was only 1.7%. Interestingly, the only women who had a rupture belonged to group 2 [β-HCG ≤5000 miu/ml]. There was no evidence of rupture in group 1 or group 3.

DISCUSSION

Non-surgical management with systemic MTX has evolved over time. Various dose regimens (single dose and 2-dose regimen) depending upon initial β-HCG levels have been adapted to increase the efficacy and accessibility of non-surgical management. Minimally invasive technique like US-guided intracardiac instillation of KCl combined with systemic MTX has further widened the spectrum of treating women desirous of non-surgical management. But there is no fixed consensus regarding which modality would be chosen for which category of tubal ectopic.

Non-surgical management has been contraindicated for tubal ectopic with larger tubal mass, high β-HCG levels and presence of FCA mainly due the risk of rupture. In this study a novel non-surgical management was devised by stratifying women into 3 different groups and 3 different regimens were individualised to treat them.

Tubal mass size accepted in most of the studies was less than 3.5- 4 cm.[10,14,22,23] In this study there was no upper limit of tubal mass size provided the women was hemodynamically stable and willing for non-surgical management as shown in the Table 1. Overall mean size of tubal mass was 2.1 cm with minimum size of 0.4 cm and maximum size of 6.4 cm.

In the present study fetal cardiac activity (FCA) was present in 24.13% of women, which was significantly higher than in previous studies.[14, 22] Stovall and Ling reported fetal cardiac activity in 11.7% women receiving single dose MTX treatment.[22] Wang et al reported the presence of FCA in 3.9% women in their study group.[14] The higher incidence of FCA may be due to be the diagnosis was made late or the women were referred from peripheral hospitals which delayed the diagnosis.

Presence of minimal amount of free fluid in the women who were treated with non-surgical management varied from 28-56%. [24,25] In comparison in this study percentage population who had free fluid in pelvis was 51.72%.

Success rate of US guided intracardiac KCl and systemic MTX (group 1) in the present study was compared with that of other similar studies.

Apparent success rate (78.6%) in this study was marginally lesser than that of the other studies.[14] But minimally invasive technique is quite safe and can be considered an option to treat live tubal ectopic pregnancy in women not desiring surgery after explaining the possibility of future repeat ectopic and the tubes functional capacity for future reproduction being compromised.

Success rate in women who had initial β-HCG ≤5000 (group 2) and received single dose was 93.1%. The largest retrospective study till date by Lipscomb et al also reported a success rate of 91.5% who received single dose regimen of systemic MTX.[21] Comparable success rates of 94% was reported in earlier studies.[22] However they included women who had initial very low β- HCG levels in the range of ≤1500 miu/ml.

Potter et al and Elito et al have reported failure rates of 57% and 62% with initial β-HCG levels ≥5000 IU/L.[26,27] Menon et al reported after a systemic review of several observational studies that failure rate was >14.3%, if initial β-HCG levels was >5000 miu/ml whereas only 3.7% if initial β-HCG level was<5000 miu/ml.[28] So, to conclude from the above references, in women with higher trophoblastic cell load and β-HCG ≥5000 miu/ml failure rate increased with single dose regimen of MTX.

In the present study women who had initial β-HCG levels ≥ 5000 miu/ml were treated with 2-dose regimen (group 3) with success rate of 92.3%. The first prospective study on 2-dose regimen was conducted by Barnhart et al in which a success rate of 87% was reported. Hamed et al in a randomised control trial reported success rate of 77.5% in a similar group.[11,23] Song et al reported a success rate of 80% in women with initial β-HCG level > 5000 miu/ml who were treated with the 2-dose regimen. In this study success rate in similar group of women with initial β-HCG >5000 miu/ml was 92.3%.[29]

In contrast to this study the other studies by Barnhart et al, Hamed et al, Song et al, and Michelle et al who studied success rate of 2-dose regimen included only those women with initial β-HCG ≤15000 miu/ml and also women with initial β-HCG ≤5000 miu/ml.[11,23,29,30]

While in the present study 2 dose regimen was administered in the cohort with initial β-HCG≥5000 miu/ml without any fixed upper limit. Success rate in this study with an intention to treat basis was 86.21%. Actual success rate after excluding the women who had opted out was 89.3%.

The women who completed the treatment protocol in this study were stratified according to five initial β-HCG ranges irrespective of the treatment received (Table 2) there was no linear relationship between initial β-HCG level and treatment outcome. It is possible that 3 different regimens chosen to treat 3 categories of tubal ectopic had blunted the effect of increased trophoblastic activity evidenced by high β-HCG levels.

Tubal rupture rate with Non-surgical management was only 1.7% in the present study. Barnhart et al and Hamed et al had reported a rupture rate of 3% and 2.5% respectively. Interestingly, the only women who had rupture belonged to group 2 (initial β-HCG≤5000 miu/ml).[11,23]

CONCLUSION

Not all women with tubal ectopic pregnancy are similar. They differ in location of tubal ectopic, initial β-HCG, size of ectopic mass, presence or absence of fetal cardiac activity. Women who are offered non-surgical management have to be properly selected and counselled. Treatment regimen of non-surgical management should be individualized.

In this experimental study we attempted to optimise the various regimen of non-surgical management available at our institute to suite different category of women with tubal ectopic pregnancy. We concluded that in hemodynamic ally stable women with unruptured tubal ectopic pregnancy even with advanced gestation of ectopic pregnancy, high initial β-HCG levels, presence of fetal cardiac activity and larger tubal mass size high success rate could be achieved without compromising safety. The main drawback of the study was a small sample size. A larger population with live ectopic pregnancy should be studied for a robust experience of success of US guided intra-cardiac KCL and systemic MTX. Likewise, the success of 2-dose regimen with a higher trophoblastic cell load and β-HCG≥5000 miu/ml without FCA.

The present study is not a comparative analysis between the three modalities of non-surgical management. We tried to reach a consensus about when to administer single dose and 2-dose regimen. Minimally invasive technique (US guided KCl and systemic methotrexate) can be used with caution in women desirous of future fertility or who have previous history of salpingectomy without compromising the tube and ovarian reserve.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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