Original Article

Indian Journal of Obstetrics and Gynecology
Volume 5 Number 1, January - March 2017
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.5117.1

Local Ultrasound Guided Intra-Embryonic KCL Instillation with Systemic Methotrexate Versus Methotrexate Alone in Management of Live Tubal Ectopic Pregnancy: A Case Series

Nutan Agarwal*, Vidushi Kulshrestha, Alka Kriplani*, Neerja Bhatla***

Abstract

Objective: To compare efficacy of systemic methotrexate with concurrent intra-embryonic potassium chloride (KCl) instillation versus systemic methotrexate alone in cases of live unruptured ectopic pregnancies.

Method: In this retrospective comparative study conducted in tertiary care centre; six patients with documented cardiac activity suitable for medical management were given ultrasound-guided intra-embryonic KCl along with systemic methotrexate (Mtx) (Group-1). Their response was compared with six historical cases managed with systemic Mtx alone (Group-2).

Results: Medical management was successful in 100% patients in Group-1 treated with combined KCl and Mtx, all responded to only single dose of Mtx. In Group-2, success rate was 83% where 2/6(33.3%) cases were successfully treated with single dose; 3/6(50%) patients responded to 2nd dose of Mtx and 1/6(16.7%) case had rupture. Mean duration for βhCG to become negative was 5 weeks (range 3-7 weeks) in Group-1 versus 7.2 weeks (range 4-10 weeks) in Group-2.

Conclusion: Live unruptured tubal ectopic pregnancies can be effectively managed with intra-embryonic KCl and concurrent systemic Mtx therapy. Addition of KCl alleviates the need for second Mtx dose, minimizes the risk of rupture and results in faster fall of βhCG. Patients with high baseline βhCG can also be effectively treated with this combined treatment.

Keywords: Live Ectopic Pregnancy; Medical Management; Methotrexate; KCl Injection.

Synopsis: Ultrasound-guided intra-embryonic KCl instillation with systemic methotrexate may alleviate need for second Mtx dose, minimize risk of rupture and reduce follow-up with serial âhCG.

Introduction

With the advent of high resolution ultrasound and sensitive βhCG assays, ectopic pregnancy can now be diagnosed early and accurately before rupture and many women with unruptured ectopic pregnancies can be treated medically with systemic methotrexate (Mtx), thus avoiding surgery. However, presence of cardiac activity and significantly elevated βhCG, have been considered a relative contraindications to the medical management till the recent past [1]. This is because of the concerns of high failure rates, tenfold increased risk of rupture as well as the need for longer follow-up; due to significantly elevated βhCG in these patients of live ectopics. Few studies are available regarding the use of local Mtx or KCl in such cases. Due to paucity of comparative studies in literature and in absence of a consensus regarding medical management of live ectopics, these cases are often managed surgically. In view of author, this is an irony because cardiac activity in an ectopic sac confirms the unruptured status, which in itself is not a contrindication for medical

*Professor **Assistant Professor, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi – 110029.

Nutan Agarwal,
Room No. 3064 A, Teaching Block, All India Institute of Medical Sciences, New Delhi, India–110.
E.mail : nutan.agarwal1@gmail.com, nutan_agarwal@yahoo.com

Received on 16.02.2017,
Accepted on 22.02.2017

management. Besides, it is easy to localize definite ectopic sac and so ultrasound guided procedures can be preformed accurately and easily. And if direct injection of drug like KCl to the fetus achieves cardiac asystole, hypothetically, it can minimize the risk of rupture and increase chance of success even with single dose of systemic Mtx. So in this series, concurrent intra-embryonic KCl along with systemic Mtx was compared with systemic Mtx alone in live ectopic pregnancy.

Materials and Methods

This retrospective comparative study was conducted in Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India from 2001 to 2013. Cases of live unruptured ectopic pregnancies which were managed medically were reviewed from hospital records. Being retrospective study, ethical clearance was not required. Since six patients of live tubal ectopic pregnancies with documented cardiac activity were managed with ultrasound guided intra-embryonic KCl instillation with concurrent systemic Mtx (Group-1), they were compared with six controls of live tubal ectopic pregnancy managed with systemic Mtx only (Group-2). These controls were age-matched cases of live ectopics treated with systemic Mtx alone during this time frame. In all the patients, diagnosis of live ectopic was confirmed on basis of clinical findings ultrasound and serum βhCG. All patients were hemodynamically stable with confirmed ectopic gestation sac of ≤4cm size with cardiac activity and had normal hemoglobin and hematocrit, normal kidney function tests (blood urea, serum creatinine) and liver function tests (serum bilirubin, alanine and aspartate transaminases, alkaline phosphatase) and had no contraindication to Mtx therapy. All patients were thoroughly counselled for need for regular follow-ups. Medical treatment was initiated only after obtaining informed consent. Baseline βhCG was obtained and no cut-off value of baseline βhCG levels was considered a contraindication. Cases in Group-1 were managed with transabdominal ultrasound-guided 10% KCl instillation (0.5 mL initially, maximum upto 2mL) in the embryo as close as possible to the site of cardiac activity, after aspiring 0.5 mL of fluid from the gestation sac. This was followed immediately by systemic intravenous Mtx. Cardiac activity was observed on ultrasound till it stopped in Group-1. The dose of Mtx ranged between 50-75 mg when calculated as 50mg/m2 in both Groups.

βhCG was repeated on day-4 and day-7 and its fall was assessed between day-4 & day-7. No intervention was performed based on day-4 results, even if βhCG increased. A fall of 15% or more was considered successful and patients were followed weekly with serum βhCG till it turned negative. If fall in βhCG was less than 15% between day-4 & 7; second dose of intravenous Mtx was given. Outcome measures were requirement of repeat dose, failure of therapy, rupture, need for other intervention and follow up time for βhCG to become negative.

STATA 9.2 was used for analysis of data. Wilcoxon rank-sum test was used for comparison between the groups, as the data was non-parametric. P value of <0.05 was taken as statistically significant.

Results

Total six patients of live tubal ectopic pregnancy were managed with systemic Mtx with intra-embryonic KCl (Group-1) and other six cases were given Mtx alone (Group-2). Median age of patients was 30 (range 27-35), and 28(range 25-30) years respectively in Group-1 and 2 and was comparable, (p value 0.06). In Group-1, three (50%) patients had previous live issue, two (33.3%) were primigravida and one (16.7%) had history of previous loss. In Group-2, three (50%) patients were primigravida and 3(50%) had history of previous losses. Three patients in Group-1 had risk factors for ectopic with history of previous ectopic in one patient, history of infertility and ATT in one and intrauterine device in situ in one patient. In Group-2, four (66.7%) patients had risk factors with history of previous ectopic in two patients, history of infertility in one and history of tuboplasty in one patient. Mean sac size was 23.6 (range 10-34) and 25.7 (range 14-40) mm respectively in two groups which was comparable (p value 0.75). Median gestation age was 7 (range 6-8) weeks and 6.5(range 6-7) weeks respectively which was also comparable (p value 0.094) between the groups.

Mean βhCG levels at baseline, was 38532.3 ± 29466.2 (range 9536-74175) mIU/mL in Group-1 was which significantly higher than 11230.3 ± 9781.9 (range 5538-30835) mIU/mL in Group-2 (p value 0.02); as shown in Figure 1.

After first dose of Mtx, there was significant fall in βhCG in Group-1, with mean fall being 34% on day-4 and 35% from day-4 to day-7. All patients of group-1 responded to local KCl with single systemic Mtx dose by having >15% fall on day-7, hence they were followed with weekly βhCG thereafter. In contrast, βhCG increased by 19% on day-4 and by 30% from

day-4 to day-7 in Group- 2. It was because 4/6(66.7%) patients did not respond to single dose and required second Mtx dose. Even in the 2/6(33.3%) patients who did respond to single Mtx dose, βhCG fall was only1.23% on day-4 and 15.8% on day-7 which was substantially lesser than Group-1. Overall, 100% patients responded to single dose Mtx with local KCl compared to only 33.3% with single dose Mtx alone.

After second Mtx dose in group-2, there was 7.6% rise in βhCG on day-4. One patient had rupture on day-5 for which salpingectomy was done. Rest 3 patients responded with 48.6% mean fall at day-7 with no further intervention needed in any patient, thereafter.

Initial rate of fall, between week 1 and week 3, was steep (70-80%) in KCl group compared to only 45-70% in Group-2. However, further fall was almost similar in both groups (Figure 2). Mean duration for βhCG to become negative after the response with medical management was 5 weeks (range 3-7 weeks) in group-1 versus 7.2 weeks (range 4-10 weeks) in Group 2 (p value 0.18) (Figure 2). However, total duration of follow-up from the initiation of medical treatment till βhCG turned negative was 6 weeks in Group-1 versus considerably higher 8.8 weeks in Group 2. Details of individual cases from recruitment to follow-up is given in Table 1.

Table 1: Subject-wise details of medical management in live ectopic pregnancy

Group	Sac size (in mm)	Baseline βhCG (in mIU/mL)	Fall on Day-4	Fall between Day 4 & 7	2nd Mtx dose needed	Baseline βhCG for 2nd dose (in mIU/mL	Fall on Day-4 for 2nd dose	Fall between Day 4 & 7 for 2nd dose	Duration from response till negative βhCG (in weeks)	Total follow-up(in weeks) from initiation of treatment till negative βhCG
Group-1 (Mtx + KCl)	10	54180	15.6%	34.6%	-	-	-	-	6	7
	20	65923	22.8%	15.1%	-	-	-	-	6	7
	28	74175	26.1%	44.4%	-	-	-	-	7	8
	20	14290	50.5%	31.6%	-	-	-	-	5	6
	34	13090	14.2%	52.9%	-	-	-	-	3	4
	30	9536	75.2%	33.3%	-	-	-	-	3	4
Group-2 (Only Mtx)	14	5897	40.3%	19.9%	-	-	-	-	6	7
	40	5538	-91.7%*	-1.7%*	Yes	7804	27%	28%	4	6
	15	6635	25.1%	-8.6%*	Yes	1993	63%	68%	6	8
	30	10685	-48.8%*	-157.5%*	Yes	42100	-5.2%*	48%	10	12
	25	7792	-5.8%*	-51.5%*	Yes	19400	-55.2%*	Ruptured	-	-
	30	30835	-37.8%*	15.2%	-	-	-	-	10	11

*Minus values indicates rise in βhCG
Mtx- Methotrexate

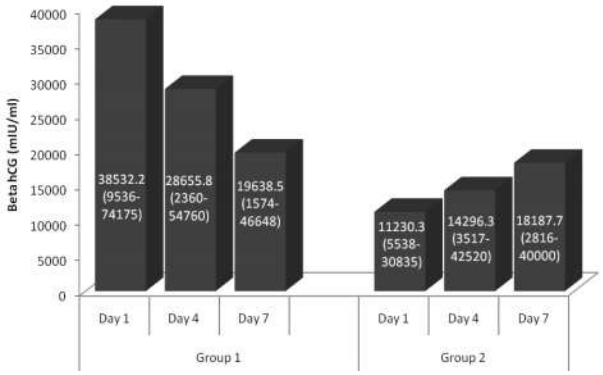

Fig. 1: Mean âhCG at baseline, Day 4 and day 7 in the two groups

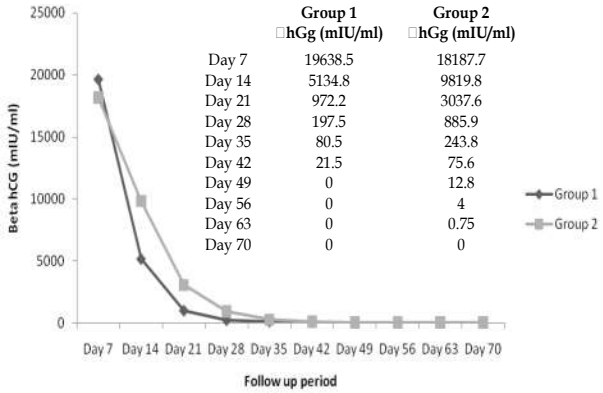

Fig. 2: Weekly fall in âhCG after response with medical treatment in group 1(n=6) and 2(n=5)

Discussion

Approaches used in medical management of live ectopic include systemic Mtx, local Mtx, and combined systemic Mtx with local KCl or Mtx. First case of medical management of live ectopic was reported by Kaplan & Brandt in 1989, which was treated with alternate Mtx and folinic acid regime with four doses of each. However, the patient needed tight intracervical and vaginal pack with indwelling catheter on day-25 due to excessive bleeding, as this was a cervical ectopic pregnancy [2]. First study which documented effect of single dose systemic Mtx on live ectopic of less than 3.5cm size, showed efficacy of 79.5% with 11.4% risk of rupture; however, baseline âhCG was not mentioned [3].

There have been individual case reports mentioning use of local KCl for managing live tubal ectopic pregnancy [4,5,6]. In a series by Tzafettas et al, where transvaginal intrasac high dose local Mtx (100mg) was given in 79 patients including 34 live ectopics, 79.4% success was reported among live ectopics, although additional KCl injection was given in 7 patients with persistent cardiac activity on day-7. Mean baseline βhCG in this series was only 6844mIU/mL and sac size included was <3.5cm. This high success might be due to the high dose used [7].

This was followed by few case series where local KCl was used for managing live cervical and tubal ectopic pregnancy [8-14]. Jeng et al treated 22 live cervical ectopics with transvaginal intra-amniotic and intrachorionic Mtx along with intracardiac KCl, βhCG declined to <5 mIU/mL within mean of 38 days [9]. Verma et al reported success in all 15 live cervical pregnancies treated with systemic Mtx with intracardiac KCl [10].

There are case reports of managing live tubal ectopics having < 2.5 cm sac size with transvaginal ultrasound guided intrasac KCl injection with systemic Mtx [11,12]. In a series by Monteagudo et al, 18 live ectopics including four tubal pregnancies were treated with transvaginal ultrasound guided local Mtx (n=8) or KCl(n=10) using automated puncture device in the sac. Both the drugs had similar resolution of ectopic pregnancy [13].

In a recently published retrospective study15 similar to our study, 73% live tubal ectopics were successfully treated with systemic Mtx alone, whereas higher success rate of 93% was achieved with systemic Mtx combined with local KCl/Mtx; 95% with KCl (n=21) and & 91% with Mtx (n=24), p=0.03.14 This success rate is similar to our study where 100% patients responded to concurrent treatment with single dose systemic Mtx with local KCl compared to only 83.3% with Mtx alone.

In the present series, we included sac size upto 40mm, with no limit to βhCG levels. A systemic review by Menon & Colins suggested that multiple dose of Mtx may be more appropriate if βhCG is more than 5000 mIU/mL as single dose has upto 14.3% failure rate in such cases versus 3.7% if βhCG is less than 5000 mIU/mL15.However, in the present series, all the patients in group-1, had baseline βhCG >9500 (9536-74175)mIU/mL which was significantly higher than Mtx only group. Despite this, none of the patients needed the 2nd Mtx dose and none had rupture. ASRM16 does not recommend medical treatment in βhCG >5,000 mIU/mL and the latest review article also recommends triaging only 'less active' ectopic for medical management with βhCG <5,000 mIU/mL and absent fetal cardiac activity17. However our study as well as Wang's study suggest that live tubal ectopic pregnancy with high baseline βhCG can also be effectively/efficiently treated using combined local KCl and systemic Mtx. None of the 6 cases in our study managed with combined treatment required second Mtx dose, though 3 out of 21 (14%) patients in

Wang's study required second Mtx injection [14].

In group treated with Mtx alone, four(66.7%) cases did not respond to single dose and required second dose of Mtx, even though their baseline βhCG was lesser than Group-1. One(16.7%) case ruptured and had to be surgically intervened. Mean βhCG was 7662.5 mIU/mL in four patients who required two Mtx doses as compared to the mean of 18366 mIU/mL in two patients, successfully treated with one dose. This suggests that success may correlate more to the size of sac, rather than the baseline βhCG. The baseline βhCG of the patient who had rupture in Group-2 was 7792 mIU/mL before first dose and 12500 mIU/mL before 2nd dose of Mtx. Another patient in the same group with sac size of 14 mm, responded to single Mtx injection despite a baseline βhCG of 30,000 mIU/mL. Thus, the author opines that sac size may be a better predictor of success with single dose Mtx regardless of baselines βhCG titre in live ectopics.

KCl causes fetal cardiac asystole [11] with no further growth of trophoblastic tissue, thus minimizing the risk of rupture. There are no known adverse effects of KCl instillation. KCl given for managing heterotopic cervical pregnancy did not adversely affect the simultaneous viable intrauterine pregnancy, who had uncomplicated term deliveries [10], implying non-toxicity of KCl. On the other hand, Mtx has known side-effects like nausea, dizziness, mild leucocytopenia and deranged liver function tests. Single dose is exempt from complications because Mtx only affects the cells in S-phase of multiplication process [18]. However, pneumonitis, alopecia and multiple ovarian cysts have been reported with repeat Mtx doses. Addition of KCl in live ectopics may thus avoid Mtx toxicity related to repeated doses.

Time needed for βhCG to become negative has been reported from 56 to 91 days [11]. It has also been suggested in a case report that multiple doses may help in earlier resolution in live ectopics [12]. In the present series, initial rate of βhCG fall was steep in KCl group, hence βhCG became negative earlier (mean 5 weeks or 35 days) suggesting addition of KCl with single dose systemic Mtx may result in shorter period of follow-up and multiple doses of systemic Mtx can thus be avoided. Moreover, patient's total follow-up duration was also lesser with KCl, as two-third patients in Mtx only group, needed second Mtx dose which further increased the treatment period by one week. The duration of βhCG resolution was approximately 4 weeks in Wang's study where it was followed up till βhCG decreased to <20 mIU/mL, whereas in our study, patients were followed till βhCG was <1.2 mIU/mL.

In the author's opinion, live ectopic is a sure sign of unruptured ectopic. The ease of ultrasound localization of a live ectopic sac makes KCl instillation a feasible procedure. One of the limitations in the present study is the small number of cases and non-comparable baseline βhCG in the two Groups. More guarded approach was taken in the initial cases. With the successful management of live ectopics, higher and higher βhCG were considered for medical management, hence later six patients had a higher baseline βhCG. However, higher baseline βhCG did not adversely affect the outcome in this group. Larger prospective randomized controlled trials are needed to establish the efficacy of KCl in live tubal pregnancies and to further validate the role of sac size in predicting successful outcome of medical treatment of live tubal ectopic pregnancy.

Conclusion

Addition of KCl to systemic Mtx therapy may be a safe option for managing unruptured tubal ectopic pregnancies without the need for surgical intervention, hence preserving future fertility. It may alleviate the need for second Mtx dose, minimize the risk of rupture and may result in shorter duration of follow-up with serial βhCG. Patients with high baseline βhCG can also be effectively treated with this combined treatment.

Declaration of Interest

The authors declare that they have no conflicts of interest.

References

1. ACOG Practice Bulletin. Medical management of ectopic pregnancy. 2008; Number 94.
2. Kaplan BR, Brandt T, Javaheri G, Scommegna A. Successful treatment of a live cervical pregnancy with Mtx and folinic acid, A case report. J Reprod Med. 1989; 34(10):853-6.
3. Lipscomb GH, Bran D, McCord ML, Portera JC, Ling FW. Analysis of three hundred fifteen ectopic pregnancies treated with single-dose Mtx. Am J Obstet Gynecol. 1998; 178(6):1354-8.
4. Timor-Tritsch I, Baxi L, Peisner DB. Transvaginal salpingocentesis: a new technique for treating ectopic pregnancy. Am J Obstet Gynecol. 1989; 160:459–61.
5. Aboulghar MA, Mansour RT, Serour GI.

Transvaginal injection of potassium chloride and Mtx for the treatment of tubal pregnancy with a live fetus. Hum Reprod. 1990; 5(7):887-8.

6. Aruh I, Uran B, Demir N. Conservative approach in unruptured cornual pregnancy with a live fetus. Int J Gynaecol Obstet. 1997; 59:43–5.
7. Tzafettas JM, Stephanatos A, Loufopoulos A, Anapliotis S, Mamopoulos M, Kalogeropoulos A. Single high dose of local Mtx for the management of relatively advanced ectopic pregnancies. Fertil Steril. 1999; 71(6):1010-3.
8. Cipullo L, Cassese S, Fasolino L, Fasolino MC, Fasolino A. Cervical pregnancy: a case series and a review of current clinical practice. Eur J Contracep Reprod Health Care. 2008; 13(3):313-9.
9. Jeng CJ, Ko ML, Shen J. Transvaginal ultrasound-guided treatment of cervical pregnancy. Obstet Gynecol. 2007; 109(5):1076-82.
10. Verma U, Goharkhay N. Conservative management of cervical ectopic pregnancy . Fertil Steril. 2009; 91 (3):671-4.
11. Verma U, Jacques E. Conservative management of live tubal pregnancies by ultrasound guided potassium chloride injection and systemic Mtx treatment. J Clin Ultrasound. 2005; 33(9):460-3.
12. Dadhwal V, Deka D, Ghosh B, Mittal S. Successful management of live ectopic pregnancy with high beta-hCG titres by ultrasound-guided potassium chloride injection and systemic Mtx. Arch Gynecol Obstet. 2009; 280(5):799-801.
13. Monteagudo A, Minior VK, Stephenson C, Monda S, Timor-Tritsch IE. Non-surgical management of live ectopic pregnancy with ultrasound-guided local injection: a case series. Ultrasound Obstet Gynecol. 2005; 25(3):282-8.
14. Nonsurgical Management of Live Tubal Ectopic Pregnancy by Ultrasound-Guided Local Injection and Systemic Mtx Wang M, Chen B, Wang J, Ma X, Wang Y. J Min Inv Gynecol. 2014; 21:642-9.
15. Menon S, Colins J, Barnhart KT. Establishing a human chorionic gonadotropin cutoff to guide Mtx treatment of ectopic pregnancy: a systematic review. Fertil Steril. 2007; 87(3):481-4.
16. Practice Committee of American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy. Fertil Steril. 2008; 90(5):S206-12.
17. Odejinmi F, Huff KO, Oliver R. Individualisation of intervention for tubal ectopic pregnancy: historical perspectives and the modern evidence based management of ectopic pregnancy Eur J Obstet Gynecol Reprod Biol. 2017; 210:69–75.
18. Park J, Franco RS, Augsburger JJ, Banerjee RK. Comparison of 2-methoxyestradiol and Mtx effects on non-Hodgkin's B-cell lymphoma. Current Eye Research. 2007; 32(7-8):659-67.