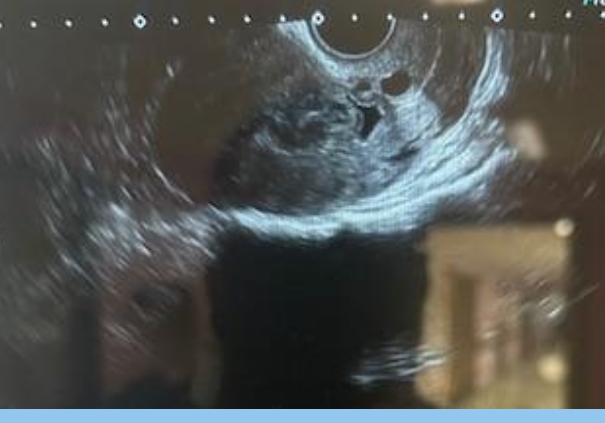


Service Evaluation On The Use Of Multiple Dose Methotrexate In The Treatment Of Ectopic Pregnancy. Authors: Dr Efosa Imuetinyan, Miss Corah Ohadike Sherwood Forest Hospital NHS Foundation Trust				
INTRODUCTION	CASE 1	CASE 4	CASE 7	LEARNING POINTS
An ectopic pregnancy is one that implant outside the uterine cavity. About 2-3% of women attending the early pregnancy unit have an ectopic pregnancy. It is a major cause of maternal mortality in early pregnancy with about 6-8 maternal deaths reported between 2006 to 2008. As more women with ectopic pregnancies present clinically stable without concern for rupture, options for treatment have expanded beyond surgical management to medical management. Medical management involves the use of methotrexate(MTX) which is a folate antagonist that binds to dihydrofolate reductase inhibiting DNA synthesis and repair. Medical management involves the use of either single dose or multiple dose of MTX. Treatment with multiple dose MTX has recognition in the management of tubal and non-tubal ectopic pregnancy. It is useful as an alternative to surgical management in patient who fertility preservation is vital. Careful follow up can be achieved to improve outcome and minimise complications. Due to its frequency of administration, the multidose protocol requires the addition of folinic acid rescue, alternating with MTX doses, to decrease its side effects. The overall success rate of multiple dose treatment in a meta-analysis by Barnhart et al is reported as 92.7%. The multiple-dose protocol is a regime adopted from MTX treatment of trophoblastic disease. Before starting MTX, women should be screened with a full blood count, liver function test, serum creatinine, blood type and Rh. Women with a history of pulmonary disease should also have a chest-Xray because of the risk of interstitial pneumonitis in patient with underlying lung disease. Liver transaminase level may go up to 20x the upper limit of the normal and this is considered safe; it spontaneously resolves after completion of treatment. It involves an 8-day regimen alternating MTX(1mg/kg) treatment with leucovorin (folinic acid 15mg PO or 0.1mg/kg IM) therapy. Methotrexate is continued until hCG falls by >15% from its peak concentration. A fall in serum hCG level by >15% requires stopping treatment and weekly surveillance until serum hCG is negative (<5mIU/mL).	41-year-old 6weeks gestation with a background of PCOS and subfertility. Presented with left sided abdominal pain and shoulder tip pain. USS -left tubal mass 14x14x11mm, no free fluids. Patient was clinically stable and declined surgery. She was given multiple dose of MTX. Pretreatment HCG- 7340 Day 3- 7047 Day 5- 6260 Day 7- 3248 LFT- normal  Total dose of MTX- 4 Outcome: laparoscopic left salpingectomy. despite falling HCG, patient symptoms worsened, and ectopic size increased to 35x30x23mm. Patient is currently being investigated for subfertility.	29-year-old 6weeks gestation with a background of Subfertility. Patient was asymptomatic, with elevated serum HCG. Scan findings showed right tubal live ectopic CRL 14.1mm with no free fluid. Indication for multiple dose methotrexate: patient was stable with a rising level of HCG. Pre-treatment HCG- 16,959 Day 3- 20,269 Day 5- 27,242  normal LFT. Total dose of MTX: 2 Outcome: right salpingectomy due to continuous rise in HCG with MTX treatment. No further pregnancy recorded.	26-year-old, 8weeks gestation with a background of 3 previous CS. Patient was asymptomatic, had a scan to confirm pregnancy location as BHCG was elevated. Scan findings showed a CS scar ectopic measuring 15x9.5x7.2mm, no free fluid. Indication for multiple dose methotrexate: CS scar ectopic pregnancy and patient was haemodynamically stable pre-treatment BHCG- 68646 Day 3- 63415 Day5- 51850 Day 7- 20332 HCG was monitored weekly till it reduced to 31  Total dose MTX- 2 Outcome: Resolution of ectopic LFT was raised post treatment but spontaneously resolved. No further pregnancy has been recorded.	- According to guidelines, weekly surveillance should be commenced after hCG level drops >15%. But in all patients, alternate day hCG monitoring continued despite fall in hCG >15%. - Weekly hCG should be continued till levels drop <5mIU/mL but in some patients, surveillance was stopped prior to having a negative hCG. This was largely due to patients not returning for follow up hCG. - An Increase in size of the ectopic is not a reason to stop multiple dose treatment if the patient is stable - An increase in HCG level is not a reason to stop the multiple dose regimen if the patient is stable - Decision for surgical management was inappropriate in case 2 and 4. an increase in size of ectopic and rise in hCG level can happen and is not indication for surgery. - These cases were not a single operator analysis, hence the disparity in management, - It has been implemented that all cases are reviewed by the early pregnancy unit lead.
	CASE 2	CASE 5	DISCUSSION	CONCLUSION
	26-year-old 6weeks gestation. With a background of PCOS and subfertility. She presented with right abdominal and shoulder tip pain. USS - right cornual ectopic pregnancy 10X9X8mm no free fluid. Indication for multiple dose methotrexate: Due to the thickness of the myometrium surrounding ectopic and likelihood of severe bleeding with surgery.  Pretreatment HCG- 5458 Day 3 -7232. LFT was normal Total dose of MTX: 2 Outcome: right salpingectomy with partial removal of right cornual of uterus as size of ectopic increased to 28x25x21mm with free fluid in POD. Patient is still under work up for subfertility.	37-year-old 10weeks gestation with a background of 2 previous LSCS. She Presented with spotting,PV. USS showed- CS scar ectopic 36x27x36mm. No free fluid. Indication for multiple dose methotrexate: Patient was stable and there was increased risk of perforation with surgery  Pretreatment HCG- 3510 Day 3- 2460 Day 5- 2233 Day 7- 1436 Normal LFT Total dose of methotrexate given: 2 Outcome: Myosure was done as weekly BHCG was static at 30-40. Patient had 1 CS delivery 2year later.	➤ Complete resolution of an ectopic pregnancy usually takes between 2-3weeks but can last as long as 6-8weeks when pretreatment hCG levels are in higher ranges. ➤ If declining hCG level rises again, the diagnosis of a persistent ectopic pregnancy is made. Therefore, patient are advised to come for follow up until hCG is negative. ➤ The importance of weekly surveillance until a negative result is achieved was evident in case 5 where a myosure for a CS scar ectopic was done as weekly hCG was static at 30-40. ➤ Methotrexate appear to be more effective when used to treat ectopic pregnancies with lower hCG as seen in case 3 and 6 where initial hCG levels were 392 and 2760 respectively and complete resolution was achieved . However complete resolution was also achieved in case 7 where initial hCG was 68,646. ➤ In case 1, the increase in size of ectopic is a normal finding and if the patient symptoms remained minimal, treatment could have been continued. ➤ In case 4, the rise in hCG could have been treated with further dose of methotrexate as the patient remained stable; it is common to see a small rise in hCG initially as is sometimes seen with single dose treatment. ➤ In this case series, treatment failure was seen in hCG levels >5,000 (42.8%) ➤ Factors predicting treatment failure in literature: i. Adnexal fetal cardiac activity ii. Size and volume of gestational mass (>4cm) iii. High initial hCG concentration (>5,000mIU/MI) iv. Presence of free peritoneal blood v. Rapidly increasing hCG concentration (>50%/48hrs) before MTX vi. Continued rapid rise in hCG concentration during MTX ➤ Although the outcome of subsequent pregnancy post methotrexate treatment in these case was only 14.2% (1 case), there was no evidence to suggest an adverse effect of MTX therapy for ectopic pregnancy on subsequent fertility or ovarian reserve.	➤ This evaluation has shown that use of multiple dose methotrexate in treatment of tubal and non-tubal ectopic pregnancy provided an effective alternative to surgical intervention where fertility preservation is important. Patient is unsuitable or decline to have surgery. The size of ectopic and hCG levels influence outcome of treatment. ➤ Due to complications that could arise from treatment with MTX, patient should be carefully selected, counselled and be able to return for follow up to monitor symptoms and hCG levels.
CASE SERIES	CASE 3	CASE 6	SUMMARY OF TREATMENT OUTCOMES	Primary References: Medical treatment of ectopic pregnancy: a committee opinion- fertility and sterility, volume 100, Issue 3, 638-644
In this case series, we analysed 7 cases of patients in their first trimester with ultrasound diagnosis of tubal or non-tubal ectopic but where hemodynamically stable, who received multiple dose of methotrexate with alternate day folinic acid. We highlighted; - Patients presenting symptoms - Type and size of ectopic on scan finding - Indication for MTX use - Number of doses administered - The outcome of treatment.	29-year-old 5weeks gestation with a background of right salpingectomy and 2 previous miscarriage. She Presented with left iliac fossa pain and PV bleed. USS scan left tubal ectopic 17x14x15mm, fluid in POD <1cm Indication for multiple dose methotrexate: Patient was clinically stable, the need for preservation of fertility as patient had a history of right salpingectomy and static HCG after 2 single doses of MTX. Pre-treatment HCG- 392 Day 3- 350 Day 5- 336 Day 7- 56 LFT normal  Total dose of MTX: 2 outcome: resolution of ectopic pregnancy. No further pregnancy recorded.	35-year-old 7weeks gestation with a background of 2 previous miscarriage and1 MTOP Presented with RIF pain No ectopic was seen on scan HCG was fluctuating between 2500 to 3000 Indication for multiple dose methotrexate: Patient was stable, PUL with fluctuating levels of BHCG  Pre-treatment BHCG- 2760 Day 3- 1597 Day 5- 921 Day 7- 61 Total dose of MTX- 1 Outcome: resolution of ectopic LFT was raised post methotrexate but spontaneously resolved Subsequently, the patient had a salpingectomy for a right tubal ectopic and in the same year also had a left tubal ectopic managed with single dose methotrexate.		
			43%(3 cases) had resolution of ectopic with multiple-dose methotrexate. 57%(4 cases) required surgery. - Average(mean) dose of MTX given that achieve resolution : 2 85.7%(6 cases) of patient did not require 8 full Day regimen. 28.5(2 cases)- raised in ALT which spontaneously resolved. 14.2%(1 case)- patient had intrauterine pregnancy 2 years post treatment	