Health Western Sydney Local Health District | Women's & Newborn Health Westmead Hospital

RANZCOG 2021 Virtual Annual Scientific Meeting 15–18 February

The authors would like to thank RANZCOG for their financial support of this study through the RANZCOG Travel and Research Grant supported by Ferring Pharmaceuticals.

Day 1 to Day 4 serum hCG change in predicting single-dose methotrexate treatment failure for tubal ectopic pregnancies

Goh A[1,3], Karine P[1], Kirby A[2], Williams C[1], Kapurubandara S[1,3]

[1]Department of Obstetrics and Gynaecology, Westmead Hospital, Sydney, Australia [2]NHMRC Clinical Trials Centre at The University of Sydney, Sydney, Australia
[3]The University of Sydney School of Medicine, Sydney, Australia

Citation: *Eur J Obstet Gynecol Reprod Biol*. 2020;225:105-110

Introduction

Medical management with methotrexate (MTX) is considered to be a safe, effective, and economical alternative to surgery in stable cases of ectopic pregnancy (EP)[1-3]. In 1991 Stovall[1] first described the outpatient regimen of single-dose MTX for unruptured EPs. The study defined treatment success as ≥15% drop in Day 4 to Day 7 (Day 4/7) hCG levels after single-dose MTX, and this definition is still the gold-standard[1,3]. A disadvantage of this protocol, however, is the anxiety created with the rise in hCG that is often seen on Day 4[1]. The already-worried patients must wait until Day 7 before the effectiveness of the MTX can be assessed to determine if additional MTX or surgery is required. This study aims to determine if trends in Day 1 to Day 4 (Day 1/4) serum hCG levels can predict treatment failure of single-dose MTX in the medical management of tubal EPs.

Method

This retrospective cohort study was conducted at a tertiary hospital. Files were reviewed for all women who received at least one dose of 50mg/m^2 intramuscular MTX for treatment of ultrasound-confirmed tubal EPs between 2013 and 2018. "Treatment failure" is defined as needing additional MTX or surgery to manage the EP.

References

[1]Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. Obstet Gynecol 1991; 77:754-7

[2]Nguyen Q, Kapitz M, Downes K, Silva C. Are early human chorionic gonadotropin levels after methotrexate therapy a predictor of response in ectopic pregnancy? Am J Obstet Gynecol 2010; 202: 630e1-5.

[3]Kirk E, Condous G, Van Calster B, et al. A validation of the most commonly used protocol to predict the success of single-dose methotrexate in the treatment of ectopic pregnancy. Human Reprod 2007; 22: 858-863.

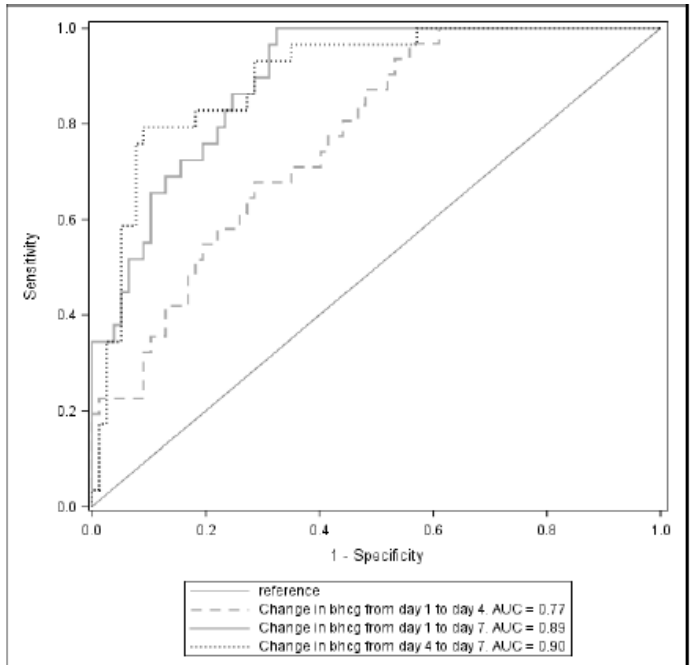

Figure _. Receiver-operator characteristic curves for the prediction of treatment failure of single-dose methotrexate for tubal ectopic pregnancies, showing the percentage change in Day 1/4, Day 1/7, and Day 4/7 serum human chorionic gonadotropin levels.

Table Different hCG changes in demonstrating treatment failure of single-dose methotrexate therapy.

hCG change	Area Under Curve (95%CI)	*p*-value AUC	Threshold value	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Day 1/4	0.77 (0.68-0.86)	<0.001	+5%	68% (49-83)	69% (56-78)	46% (36-56)	84% (75-90)
Day 1/7	0.89 (0.84-0.95)	<0.001	-10%	76% (56-90)	79% (68-88)	58% (46-69)	90% (82-94)
Day 4/7	0.90 (0,.84-0.96)	<0.001	-17%	83% (64-94)	82% (71-90)	63% (51-74)	93% (85-97)

Abbreviations: hCG, human chorionic gonadotropin; 95%CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value

Results

108 patients were included for final analysis. 17% of cases required additional MTX and 12% required surgery to manage the EP. ROC analysis of Day 1/4 hCG demonstrates that ≥5% rise best predicts failure with sensitivity 68%, specificity 69%, and AUC 0.77, *p<0.001* (**Figure**). Applied retrospectively to the study cohort, ≥5% rise in Day 1/4 hCG identifies 46/108 women as failures, whereas the gold-standard 15% drop in Day 4/7 hCG identifies 30/106 women. Of the 46 identified women, 21 (46%) were confirmed failures. If all 46 women had been given a second dose of MTX on Day 4, 25 women would have received the second dose unnecessarily as they would have been successful with just the single dose, i.e. PPV 46% (95%CI 36-56%), and NPV 84% (95%CI 75-90%) (**Table**).

Ten women with Day 1/4 hCG rise <5% and seven women with Day 4/7 drop >15% failed treatment, indicating that there are other unidentified factors contributing to unsuccessful treatment.

Discussion

This study suggests that ≥5% rise in Day 1/4 serum hCG levels could potentially predict failure of single-dose MTX for tubal EPs, and that conversely, <5% rise or any drop in Day 1/4 hCG levels can reliably predict success. The ability to provide reassurance or counsel about further intervention options on Day 4 could reduce patient anxiety associated with waiting. Clinicians could consider consider factoring-in Day 1/4 hCG changes during the course of medically managing patients, bearing in mind, however, that this could lead to increased interventions.