

Management of uterine ectopic pregnancy – local vs. systemic methotrexate

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Key words

Methotrexate, uterine ectopic pregnancies, cervical pregnancy, interstitial pregnancy, cesarean section scar pregnancy, beta hCG clearance duration

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Koch M, Schwab S, Meyer E, Montanari E, Bader Y, Ott J, et al. Management of uterine ectopic pregnancy – local vs. systemic methotrexate. *Acta Obstet Gynecol Scand* 2018; 97:824–829.

Received: 26 November 2017

Accepted: 14 March 2018

DOI: 10.1111/aogs.13348

Abstract

Introduction. The aim of this study was to compare ultrasound-guided local methotrexate (MTX) vs. systemic methotrexate in uterine ectopic pregnancy regarding the beta human chorionic gonadotropin (hCG) clearance duration. **Material and methods.** Patients with interstitial pregnancy, cervical pregnancy or cesarean scar pregnancy were included. Methotrexate was administered locally ultrasound-guided (25 mg methotrexate fixed dose) or systemically (intramuscular; 50 mg/m² body weight). Beta hCG clearance duration in days formed the main outcome measure. **Results.** Forty-six patients with uterine ectopic pregnancy were included. The mean estimated beta hCG clearance duration was 29.2 days longer in patients with local methotrexate compared with systemic methotrexate (64.7 vs. 31.5 days, respectively; $p = 0.026$). There was no significant difference between local vs. systemic methotrexate regarding adverse events such as bleeding ($p = 0.376$), pain ($p = 0.146$) or secondary surgery ($p = 0.631$). There was no association of initial beta hCG levels ($p = 0.746$), initial progesterone levels ($p = 0.870$) or patients' age ($p = 0.604$) and the beta hCG clearance duration. No significant difference in beta hCG clearance duration comparing local methotrexate injection with aspiration vs. local methotrexate injection without aspiration could be found (mean 49.4 and 71.6 days, respectively, $p = 0.225$). **Conclusions.** In patients with uterine ectopic pregnancies, the mean estimated beta hCG clearance duration was 29.2 days longer when applying local methotrexate compared with systemic methotrexate.

Abbreviations: hCG, human chorionic gonadotropin; MTX, methotrexate.

improvements in both scanning machines and scanners,

Introduction

In all, 1–2% of all pregnancies are ectopic (1,2). Although most of them are of tubal origin, about 7% of all ectopic pregnancies are considered non-tubal ectopic pregnancies and include ovarian, abdominal, interstitial, cervical and cesarean scar pregnancies (3,4).

Because they are rare, those pregnancies are often overlooked, misdiagnosed or diagnosed late and therefore have a higher maternal morbidity and mortality than tubal ectopic pregnancies (5,6). In spite of technical

Key message

There is little evidence on the optimal treatment methods in uterine ectopic pregnancy. We compared the beta human chorionic gonadotropin clearance duration after local or systemic methotrexate application, which was found to be on average 29.2 days longer after local than systemic injection.

these rare conditions still represent a challenge in diagnosis and therapy even to experts.

Cervical pregnancies occur when the blastocyst passes the uterine cavity and implants in the cervical mucosa. They account for <1% of ectopic pregnancies, but due to the proximity to the uterine vessel, cervical pregnancies constitute a high risk for bleeding complications and have previously been treated mainly by hysterectomy (5,7). Interstitial pregnancies make up 1–11% of ectopic pregnancies. They are defined as pregnancies which implant in the junction of uterine myometrium and the interstitial part of the fallopian tube (5). In 6% of women with a previous cesarean section, a cesarean section scar ectopic pregnancy may occur when the blastocyst implants in the deficient uterine wall (8,9). Therapy options include expectant management, medical therapy with methotrexate (MTX) and surgical management.

Literature on the treatment of uterine ectopic pregnancy is scarce; however, MTX either systemically or locally is suggested as a first-line treatment in uncomplicated cervical or interstitial pregnancy (10–12). For cesarean scar pregnancy, local MTX injection is preferred to systemic injection, as complication rates seem lower (13–15).

The objective of this study was to compare treatment options (ultrasound-guided local MTX vs. systemic MTX) in uterine ectopic pregnancy (cesarean scar pregnancy, cervical pregnancy and interstitial pregnancy) regarding the duration of beta human chorionic gonadotropin (hCG) clearance.

Material and methods

All women with uterine ectopic pregnancy (interstitial pregnancy, cervical pregnancy or cesarean scar pregnancy) who were given transvaginal ultrasound by one expert sonographer at our Department of Gynecologic ultrasound between 2008 and 2015 were included in this study. A total of 5446 ultrasound examinations were documented by one expert sonographer in this time period. Of these, 267 were diagnosed ectopic pregnancies (4.9%), with a majority being tubal ectopic pregnancies. Treatment options comprised expectant management, MTX and surgery. MTX was administered either locally ultrasound-guided (25 mg MTX as fixed dose) (15,16) or systemic (intramuscular; 50 mg/m² body weight). MTX was applied systemically if initial beta hCG (human chorionic gonadotropin) levels were <5000 mIU/mL (17–19). If initial beta hCG levels were >5000 mIU/mL, local MTX injection was applied. Expectant management was chosen if initial beta hCG levels were >1500 mIU/mL and had declined by >15% within 48 h.

Beta hCG clearance duration formed the main outcome measure, defined prior to data retrieval. Transvaginal ultrasound for diagnosis of uterine ectopic pregnancy was done by one expert sonographer in all cases. Ultrasound criteria for diagnosis were the following:

Cervical pregnancy: empty uterine cavity, barrel-shaped cervix, gestational sac located below the uterine arteries, absent sliding sign, present Doppler flow around the gestational sac.

Cesarean scar ectopic pregnancy: empty uterine cavity, gestational sac located anteriorly at the level of the internal os covering the visible or presumed site of the cesarean section scar (lower uterine segment), evidence of functional trophoblastic/placental circulation on Doppler flow, negative sliding sign.

Interstitial pregnancy: visualization of the interstitial line adjoining the gestational sac and the lateral aspect of the uterine cavity and continuation of the myometrial mantle around the gestational sac.

Patient data were retrieved from the software VIEW POINT, Version 5.6.5.319 (GE Healthcare, Little Chalfont, UK). Beta hCG levels were measured in all patients until beta hCG clearance (<20 mIU/mL) (20).

To investigate whether the management (systemic MTX or local MTX) has a significant impact on the beta hCG clearance duration, a Wilcoxon test at significance level $\alpha = 0.05$ was conducted. To further assess the influence of initial hCG, initial progesterone and age on the hCG clearance duration, a linear regression with these confounders, as well as the management as independent variable, was computed. Calculated *p*-values for the secondary endpoint analyses served only descriptive purposes and therefore no multiple testing corrections were applied. To investigate the effect of the management (systemic MTX or local MTX) on adverse effects, Fisher's exact tests were conducted. To investigate whether the management (systemic MTX vs. local MTX with aspiration and systemic MTX vs. local MTX without aspiration) had a significant impact on the hCG clearance duration, a Kruskal–Wallis test was conducted. Local MTX treatment with prior aspiration included aspiration of the entire fluid content of the gestational sac to reduce the volume of the pregnancy as much as possible. Pairwise comparisons were performed using Dunn's test. Statistical analysis was done using R (The R Foundation, <https://www.r-project.org>).

Ethical approval

Ethical Review Board approval was obtained from the Ethics Committee of the Medical University of Vienna (2052/2015). Informed consent could be waived due to the retrospective study method.

Results

Data of 46 patients with uterine ectopic pregnancy were available for analysis. Twenty-four were cesarean scar pregnancies, 17 interstitial pregnancies and five cervical pregnancies.

Of these 46 patients, two (4.3%) were treated with expectant management, 15 (32.6%) received systemic MTX, 24 (52.2%) received local MTX (17 without aspiration, seven with aspiration) and five (10.9%) received primary surgery. Two patients in the systemic MTX group and six patients in the local MTX group had to be excluded due to missing data.

For the primary endpoint analysis, therefore, 13 patients with systemic MTX and 18 patients with local MTX could be included. The mean age of all patients was 33 years (min. 23, max. 55). There was no significant difference in mean age when comparing the local and systemic MTX group (31 years $\pm$ 5 SD and 35 years $\pm$ 8 SD, respectively, $p = 0.136$).

Mean number of pregnancies was 3.6 ($\pm$ 2.4 SD), mean parity was 1.2 ($\pm$ 0.9 SD) and mean number of previous cesarean sections (CS) was one ($\pm$ 0.9 SD). In patients with cesarean scar pregnancy, the mean number of previous CS was 1.4 as compared with 0.3 in interstitial and cervical pregnancy, respectively.

The mean duration until beta hCG clearance was 54 days (min. 13, max. 140). Eleven percent of patients reported moderate abdominal pain and 15% reported vaginal bleeding during MTX treatment. None of the patients reported pain or bleeding prior to MTX treatment. Subjectively reported abdominal pain during MTX treatment was not associated with intraperitoneal hemorrhage. Four patients (9%) received secondary surgery after MTX treatment due to severe vaginal bleeding and rising serum beta hCG levels.

The distribution of type of uterine ectopic pregnancy and therapeutic management is displayed in Table 1.

Patients who received local MTX had a significantly longer beta hCG clearance duration compared with patients who received systemic MTX (64.7 vs. 31.5 days, respectively; $p = 0.026$). The mean estimated beta hCG clearance duration was 29.2 days longer in patients with local MTX.

Beta hCG clearance curves are illustrated in Figures 1 and 2. There was no significant difference between local vs. systemic MTX regarding adverse events such as bleeding ($p = 0.376$), pain ($p = 0.146$) or the necessity of secondary surgery ($p = 0.631$). Absolute frequencies of adverse events are displayed in Table 2.

Even though nonsignificant, we observed more adverse events in the local MTX treatment group.

Table 1. Total number of uterine ectopic pregnancies and their respective management.

	Cesarean section scar pregnancy Count	Interstitial pregnancy	Cervical pregnancy
Management			
Expectant	0	2	0
Systemic methotrexate	4	9	2
Local methotrexate	17	5	2
Surgery	3	1	1
Total count $n = 46$	24	17	5

There was no association of initial beta hCG levels ($p = 0.746$), initial progesterone levels ($p = 0.870$) or the patients' age ($p = 0.604$) with the beta hCG clearance duration. While there was an overall difference between the three management options systemic MTX vs. local MTX with aspiration vs. local MTX without aspiration, no significant difference in beta hCG clearance duration could be found comparing local MTX injection with aspiration vs. local MTX injection without aspiration (mean days 49.4 and 71.6, respectively, $p = 0.225$).

The mean beta hCG clearance duration comparing local vs. systemic MTX was 74 vs. 47 days, 29 vs. 24 days and 93 vs. 57 days for cesarean section scar pregnancy, interstitial pregnancy and cervical pregnancy, respectively.

Discussion

Evidence on the optimal management of uterine ectopic pregnancy (cervical pregnancy, interstitial pregnancy and cesarean section scar pregnancy) seems scarce.

In our study, we found a significantly longer duration of beta hCG clearance in patients who received local MTX (ultrasound-guided) than systemic MTX. The mean estimated beta hCG clearance duration was 29.2 days longer in patients with local MTX.

Our findings seem to contradict previous studies which postulated better treatment success with local MTX injection in cesarean scar pregnancy due to a lower rate of adverse events (14,15). On the contrary, we observed more adverse events in the local MTX treatment group, although these findings were nonsignificant. Overall, we found no significant difference in the occurrence of bleeding, pain or the necessity for secondary surgery when comparing local vs. systemic MTX treatment.

Strengths of this study include the relatively large sample size compared with previous studies. Furthermore, all ultrasound examinations and all ultrasound-guided local MTX injections were performed by one

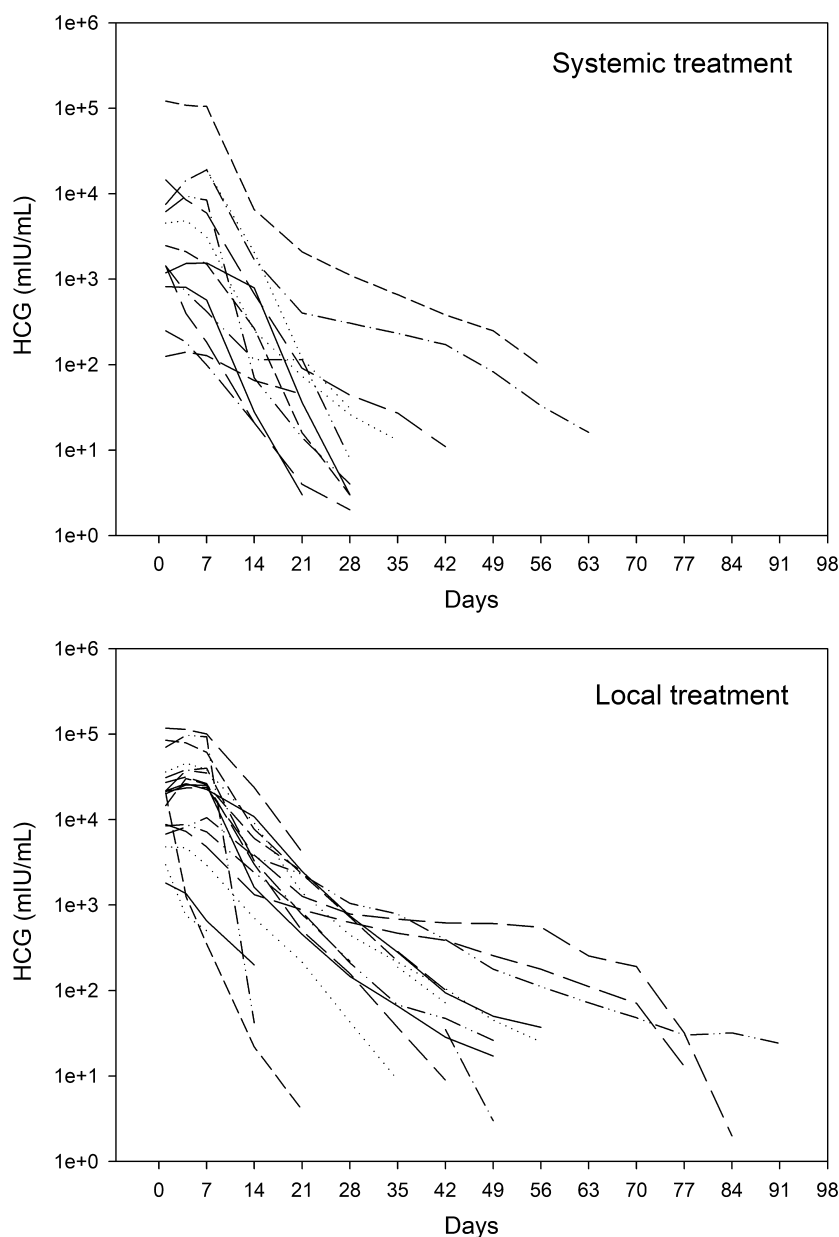


Figure 1. Logarithmic beta human chorionic gonadotropin (hCG) clearance curves comparing local vs. systemic methotrexate treatment. Day 0 = Day of methotrexate treatment.

expert sonographer, which precludes a potential interobserver bias. One limitation of this study may be its retrospective design and the concomitant evaluation of beta hCG clearance duration in interstitial, cervical and cesarean section scar pregnancy. Four cesarean section scar pregnancies, nine interstitial pregnancies and two cervical pregnancies were treated with systemic MTX, whereas 17 cesarean section scar pregnancies, five interstitial pregnancies and two cervical pregnancies were treated with local MTX. When looking at the individual

beta hCG clearance, we observed a reduced number of days until beta hCG clearance in patients with interstitial pregnancy than with cesarean section scar pregnancy or cervical pregnancy. However, in all types of uterine ectopic pregnancy, local MTX treatment resulted in a longer beta hCG clearance duration than systemic MTX, which is the main outcome of this study. As the criteria for local MTX were an initial beta hCG level of >5000 mIU/mL, this may explain a longer beta hCG clearance duration. However, there was no association of initial

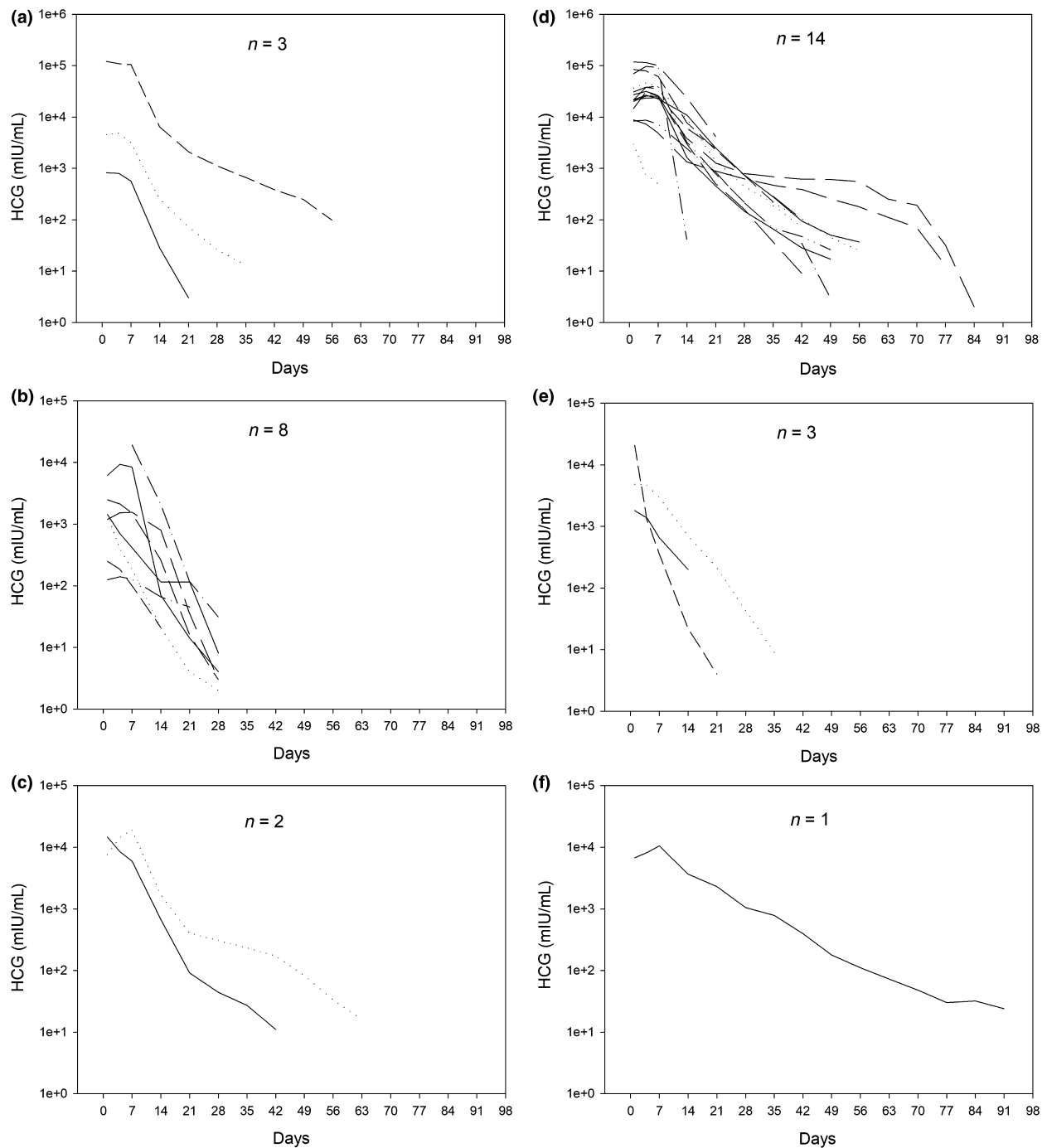


Figure 2. Logarithmic beta human chorionic gonadotropin (hCG) clearance curves by type of uterine ectopic pregnancy (interstitial, cervical, cesarean scar pregnancy) and respective methotrexate treatment (local vs. systemic). Systemic methotrexate treatment: (a) cesarean scar pregnancy, (b) interstitial pregnancy, (c) cervical pregnancy. Local methotrexate treatment: (d) cesarean scar pregnancy, (e) interstitial pregnancy, (f) cervical pregnancy. Day 0 = Day of methotrexate treatment.

beta hCG levels ($p = 0.746$) and the beta hCG clearance duration.

In conclusion we found a significantly longer duration of beta hCG clearance in patients with uterine ectopic

pregnancy (cesarean section scar, interstitial, cervical) who received ultrasound-guided local MTX compared to systemic MTX. The mean estimated beta hCG clearance duration was 29.2 days longer in patients with local

Table 2. Absolute frequency of adverse events.

	Absolute frequency of adverse events		
	Bleeding	Pain	Secondary surgery
Systemic methotrexate	1	0	2
Local methotrexate	5	4	2

MTX. No difference was found in beta hCG clearance duration comparing local MTX with aspiration vs. local MTX without aspiration. There was also no difference in adverse events, initial beta hCG or initial progesterone level when comparing local with systemic MTX treatment.

Funding

None.

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