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ORIGINAL ARTICLE

Methotrexate treatment in progressive tubal ectopic pregnancies and hCG-related clinicosurgical implications

Askin Dogan [a,*], Ibrahim Gulhan [a], Ibrahim Uyar [a], Atalay Ekin [a], Cenk Gezer [a], Muzaffer Bilgin [b], Cüneyt E. Taner [a], Ibrahim E. Ertas [a]

[a] *Department of Obstetrics and Gynecology, Tepecik Education and Research Hospital, Gaziler Street, Izmir, Turkey*
[b] *Department of Biostatistics, Eskisehir Osmangazi University Medical School, Eskisehir, Turkey*

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Abstract Our aim was to evaluate the relationship between the success of methotrexate treatment and β-hCG levels in progressive tubal ectopic pregnancies. We defined a retrospective cohort of 394 progressive tubal ectopic pregnancy patients treated with methotrexate. A single-dose methotrexate protocol using 50 mg/m^2 was administered to patients with progressive tubal ectopic pregnancy. Surgery was performed in patients who exhibited signs of acute abdomen due to tubal rupture. Of 394 patients that received methotrexate treatment, 335 (84.6%) responded to medical treatment, while the remaining 59 (15.36%) underwent surgery due to treatment failure. β-hCG levels in the failure group were significantly higher as compared with the success group at Day 1, Day 4, and Day 7 (2116 ± 3157 vs. 4178 ± 3422, 2062 ± 3551 vs. 4935 ± 4103, and 1532 ± 3007 vs. 3900 ± 4783, respectively). The receiver operating characteristics curve for β-hCG levels at Day 1 was 0.738, with a cutoff value of 1418 mIU/mL, while sensitivity and specificity values reached the optimum for treatment success (83.1% and 59.4%, respectively). Medical treatment with methotrexate achieved an 85.02% success rate for the treatment of progressive tubal ectopic pregnancy, while success rates for medical treatment decreased significantly when initial β-hCG levels were >1418 mIU/mL.

Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Obstetrics and Gynecology, Tepecik Education and Research Hospital, Gaziler Street, Number 468, 35120, Izmir, Turkey.
E-mail address: askindoganmd@gmail.com (A. Dogan).

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Introduction

Ectopic pregnancy (EP) occurs in ~1–2% of all pregnancies [1]. Assisted reproductive techniques, a history of pelvic inflammatory disease, tubal surgery, and a history of EP are established risk factors for EP [2]. Patients showing a decline or plateau in β-hCG levels are managed expectantly. In hemodynamically stable patients, treatment during this period involves medical therapy if the β-hCG levels plateau or increase. In hemodynamically unstable patients with signs of acute abdomen or rupture of EP, the only treatment choice is surgery [3].

Medical treatment includes the use of methotrexate, which is currently used worldwide and is the most efficient agent. Methotrexate is preferred, because it has few side effects and high efficiency. Various administration protocols are used in clinical practice involving single-, two-, and fixed-dose regimens [3]. Monitoring serial β-hCG levels and the clinical findings associated with tubal rupture, such as hemodynamic instability and severe pain, are helpful in evaluating the efficacy of medical therapy. Serial β-hCG monitoring can also be used to differentiate spontaneously resorbing EP from progressive EP. Single-dose methotrexate is the most common treatment protocol, with the main purpose being achieving maximum success from administering the lowest dose possible with minimal side effects.

This study investigated the success of methotrexate therapy and factors affecting treatment success in patients with progressive tubal ectopic pregnancy (PTEP).

Methods

This retrospective study was conducted at Department of Obstetrics and Gynecology, Tepecik Education and Research Hospital, and approval was obtained from the institutional ethics committee. The medical records of patients with tubal EP between January 2009 and September 2014 were reviewed retrospectively.

At our hospital, the treatment of patients pre-diagnosed with EP is guided by a treatment protocol in which hemodynamically stable patients are monitored with serial β-hCG measurements and ultrasonography. Patients with a $>$ 15% daily decrease in serial β-hCG measurements are regarded as having spontaneously resorbing EP and monitored expectantly. Hemodynamically unstable patients with positive embryonic cardiac activity and those with signs of intra-abdominal bleeding, such as pain, undergo surgery. Patients with an inadequate increase or $<$ 15% decrease in serial β-hCG measurements are regarded as progressive EP, and endometrial curettage is performed. After endometrial curettage, daily serial β-hCG measurements are continued, and methotrexate is given to patients in whom β-hCG levels plateau (daily decrease $<$ 15%) or increase. Patients with a contraindication for methotrexate treatment (abnormal liver or kidney function tests, presence of intrauterine pregnancy, active pulmonary disease, peptic ulcer, or presence of hematological or immunological disorder) and those who request surgery undergo elective surgery.

Methotrexate treatment is tailored according to the single-dose protocol (50 mg/m^2) and administered intramuscularly after calculating the body surface area. The day of administration is regarded as Day 1, and the serum β-hCG levels are determined on Day 4 and Day 7. Patients with a $>$ 15% decrease in the β-hCG level between Day 4 and Day 7 are considered to have responded to medical therapy, and β-hCG levels are measured weekly until they fall below 5 mIU/mL. Patients who do not show a $>$ 15% decrease in β-hCG levels between Day 4 and Day 7 and whose levels plateau or increase are administered an additional dose of methotrexate (50 mg/m^2) intramuscularly. Patients with an increase in serum β-hCG levels, despite two doses of methotrexate, and those with hemodynamic instability or severe abdominal pain undergo surgery, which is regarded as indicating medical treatment failure. This study evaluated patients who were diagnosed with progressive EP according to the above-mentioned protocol and who received methotrexate. The patients in the study were divided into success and failure groups and were compared in terms of age, gravida, parity, size of EP, β-hCG levels at Day 1, Day 4, and Day 7, and the need for an additional methotrexate dose.

IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) and MedCalc 14 software packages (https://www.medcalc.org/) were used in the analysis of the study data. The continuous variables were expressed mean ± standard deviation, median (q1 – q3), and the categorical variables were expressed as percentage. The Shapiro-Wilk test was used to determine if the variables were normally distributed. The independent-sample *t* test was used in the comparison of the two groups that showed normal distributions. The Mann–Whitney *U* test was used to compare the two groups that did not show normal distributions. Receiver operating characteristic (ROC) analysis was used to determine the appropriate cut-off values for independent markers and calculate sensitivity and specificity. The level of statistical significance was established at $p < 0.05$.

Results

The study enrolled 394 patients who were admitted with a prediagnosis of PTEP, and whose diagnosis was confirmed histopathologically by endometrial curettage. As per our clinical protocol, 335 of the 394 patients who were deemed eligible for methotrexate therapy were monitored until the β-hCG levels returned to normal; this group was regarded as the success group. The remaining 59 patients underwent surgery for severe abdominal pain, acute abdomen, or hematological instability and were regarded as the failure group (Figure 1). There were no significant differences between the success and failure groups in terms of demographic and clinical characteristics (Table 1).

The β-hCG levels on day 1 were significantly lower in the patients who responded to medical treatment (2116 ± 3157 mIU/mL vs. 4178 ± 3422 mIU/mL, $p < 0.0001$). Significant differences were also seen in the mean β-hCG value between the success and failure groups at Day 4 ($p = 0.0001$) and Day 7 ($p = 0.0001$; Table 2).

ROC analysis was used to identify a specific cut-off for the maximum success rate based on these levels. ROC analyses of the Day 1 β-hCG levels revealed that the optimum cut-off point for the β-hCG level was 1418 mIU/mL (area under ROC curve = 0.738; sensitivity = 83.1%,