

Medical management of ectopic pregnancy with extremely high β -HCG levels: A case report

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Summary

We report the successful treatment of an unruptured ectopic pregnancy in a patient with extremely high β -human chorionic gonadotropin concentrations. A 33-year-old woman, gravida 2, para 0, abortus 1, presented to our department due to menstrual delay. On transvaginal ultrasonography, she had an unruptured ectopic pregnancy (3.5 x 4.5 cm). Her initial β -HCG concentration was 38,270 mIU/ml. The administration of methotrexate (50 mg/m²) was performed intramuscularly. Serum β -HCG levels decreased > 15% between post-therapy days 4 (31,324 mIU/ml) and 7 (13,108 mIU/ml), and did not rise during the subsequent weekly controls. In selected cases with unruptured ectopic pregnancy and extremely high initial β -HCG levels, medical management with a single-dose methotrexate regimen may be successful.

Key words: Unruptured ectopic pregnancy; Methotrexate; High β -HCG.

Introduction

For the medical management of unruptured ectopic pregnancy (EP), systemic methotrexate treatment is a highly attractive treatment modality. In selected cases, methotrexate therapy is cost-effective and decreases morbidity and mortality compared to laparoscopic operations. Single-dose methotrexate regimens may be used in patients with EP with high success rates [1]. However the success rate of methotrexate falls with elevated β -human chorionic gonadotropin (β -HCG) concentrations [2].

A case of ectopic pregnancy with initially high β -HCG concentrations treated successfully with single dose administration of methotrexate is described.

Case Report

A 33-year-old woman, gravida 2, para 0, abortus 1, presented to our department due to menstrual delay. She had a past history of regular menstrual cycles and had no previous history of pelvic inflammatory disease or pelvic surgery. The estimated gestational age according to the patient's last menstrual period was six weeks. There was no vaginal spotting or pelvic pain. Her pulse, blood pressure, hemoglobin level and hematocrit were normal. Transvaginal ultrasonography showed an empty uterine cavity and a gestational sac measuring 1.4 x 1.2 cm in diameter in the left adnexal region. The sac was irregular in shape and the adnexal mass on the left side had an overall size of 4.5 x 3.5 cm. Color Doppler study showed peritrophoblastic flow. There was no fluid in the pouch of Douglas. Her initial β -HCG concentration was 38,270 mIU/ml and two days later the level reached a peak of 39,498 IU/ml. Endometrial curettage was performed on the day of admission and histopathologic examination revealed no trophoblastic tissue. After discussing the treatment modalities with the patient and after obtaining written informed consent, it was decided to administer methotrexate therapy despite the high β -HCG levels. Our

patient did not have renal, hematological, or hepatic disease. The administration of methotrexate (50 mg/m²) was performed according to the most widely accepted single-dose protocol as previously published by Stovall *et al.* [1, 3] Serum β -HCG levels were measured on days 4 and 7 after the patient received 77.5 g of methotrexate. The patient was warned about the possible side-effects of methotrexate treatment such as nausea and vomiting. Serum β -HCG levels decreased > 15% between post-therapy days 4 (31,324 mIU/ml) and 7 (13,108 mIU/ml), and did not rise during subsequent weekly evaluations. The levels fell under 5 mIU/ml on the 55th day post-therapy. Serum β -HCG was measured by immunometric assay (Immulite 2000, Diagnostic Products Co., LA, USA) and standardized to the Third International Reference Preparation. Our patient did not need additional doses of methotrexate. She complained of mild nausea and dizziness. No substantial toxicity was recorded. Forty days after the patient had been discharged we observed that the mass had increased to 5.2 x 4.2 cm in size, but the mass disappeared in the following month. She had an uneventful menstrual period following therapy. Four months later, the patient spontaneously conceived, with an intrauterine pregnancy resulting in the delivery of healthy infant at term.

Discussion

For the treatment of ectopic pregnancy, expectant management may be a good choice but this approach can be considered in patients with early, small tubal gestations, with low and declining initial β -HCG levels. Laparoscopy is the surgical treatment of choice for tubal EP, but has the risk of surgical complications as well as trophoblast persistence following the surgical procedure. Although medical management of EP with methotrexate should not replace laparoscopic surgery, adequate medical management of unruptured EP may avoid unnecessary surgery and preserve the potential for future fertility.

Methotrexate, a folic acid agonist that interferes with DNA synthesis, is increasingly used for treatment of EP. The effects of methotrexate therapy on future fertility

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performance or tubal patency are similar to those of laparoscopic salpingostomy [1]. Methotrexate may be considered as single-dose or multiple-dose therapy. The reported success rate for a single-dose methotrexate regimen in the treatment of EP varies between 64% and 96%. Many physicians select patients for methotrexate therapy, on the basis of the size of the gestational mass (< 3.5 cm), absent cardiac activity, absence of peritoneal fluid and serum β -HCG level under 15,000 IU/ml. Using these criteria, methotrexate treatment is generally given to selected patients.

Initial serum β -HCG determination is one of the most useful predictors of outcome for medically treated patients. The risk of tubal rupture is increased (3 times higher) in patients with serum β -HCG > 10,000 mIU/ml. In a study by Corsan *et al.* [4] an initial serum β -HCG level under 15,000 mIU/ml had a positive predictive value for the success of single-dose methotrexate therapy of 97% and a negative predictive value of 69%. However, treatment was unsuccessful in 69% of women with serum β -HCG concentrations above that level. Lipscomb *et al.* [2] concluded that β -HCG level was the single most important factor that predicts success. These investigators treated two out of four women with methotrexate with β -HCG levels above 50,000 mIU/ml and with fetal cardiac activity, but did not report whether a single-dose or multiple-dose regimen had been administered. Stika *et al.* [5] found that women with a pretreatment β -HCG level > 50,000 mIU/ml had a greater probability of requiring surgery or multiple doses of methotrexate. In the study by Stovall and Ling [1] the maximum pretreatment serum β -HCG titer was 21,200 mIU/ml. Tzafettas *et al.* [6] treated 89% of patients with EP with single-dose methotrexate. In their series they found initial β -HCG levels as high as 46,760 IU/ml, but did not delineate the success rate of medical therapy in those cases with high β -HCG levels. In most of the studies, one of the major problems was that some authors reported the β -HCG values using the World Health Organization 2nd international standard while others used the World Health Organization 1st international standard, or did not report standards at all.

Serum β -HCG levels appear to correlate positively with the volume of the trophoblast mass and with myosalpingeal invasion. Although it is not possible to clearly understand the invasion depth of a trophoblastic mass by sonography, our patient's β -HCG level reached a peak of 39,480 mIU/ml with a total mass size of > 3.5 cm. In the

small study by Lipscomb *et al.* [2] higher serum concentrations of β -HCG were associated with high failure rates of methotrexate. However, there was no relation between the volume of the conceptus or the presence of fluid in the peritoneal cavity and the efficacy of the methotrexate treatment [2].

In our case we performed serial ultrasound scans because of the high risk of rupture evident by high initial serum β -HCG levels. The potential for emergency surgery remains an important risk. Moreover, all patients should be informed about the increased risk of treatment failure, tubal rupture, and emergency exploratory laparotomy.

In conclusion, as has been shown in our case, for an unruptured tubal ectopic pregnancy with high initial β -HCG levels medical management without surgical intervention can be successful. The patient should be informed about possible risks of that treatment modality, which may in turn, endanger her life. In addition, the patient must be informed about other treatment options (laparoscopy or laparotomy).

References

- [1] Stovall T.G., Ling F.W.: "Single-dose methotrexate: an expanded clinical trial". *Am. J. Obstet. Gynecol.*, 1993, 168, 1759.
- [2] Lipscomb G.H., McCord M.L., Stovall T.G., Huff G., Portera S.G., Ling F.W.: "Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies". *N. Engl. J. Med.*, 1999, 341, 1974.
- [3] Stovall T.G., Ling F.W., Gray L.A.: "Single-dose methotrexate for treatment of ectopic pregnancy". *Obstet. Gynecol.*, 1991, 77, 754.
- [4] Corsan G.H., Karacan M., Qasim S., Bohrer M.K., Ransom M.X., Kemmann E.: "Identification of hormonal parameters for successful systemic single-dose methotrexate therapy in ectopic pregnancy". *Hum. Reprod.*, 1995, 10, 2719.
- [5] Stika C.S., Anderson L., Frederiksen M.C.: "Single-dose methotrexate for the treatment of ectopic pregnancy: Northwestern Memorial Hospital three-year experience". *Am. J. Obstet. Gynecol.*, 1996, 174, 1840.
- [6] Tzafettas J.M., Stephanatos A., Loufopoulos A., Anapliotis S., Mamopoulos M., Kalogeropoulos A.: "Single high dose of local methotrexate for the management of relatively advanced ectopic pregnancies". *Fertil. Steril.*, 1999, 71, 1010.

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