

Can Methotrexate Induce Tubal Abortion?: A Report of Three Cases

Murat DEDE, Ümit GÖKTOLGA, Müfit Cemal YENEN, Namık Kemal DURU, Tansu KUCUK, İskender BAŞER

Ankara-Turkey

To report tubal abortion observed in laparoscopy in three tubal ectopic pregnancy cases. Laparoscopic evaluation has been made for sudden pelvic pain suggesting of clinical tubal rupture symptoms on third day following single dose of IM Methotrexate (50 mg/m^2) injection. Tubal abortion was observed in all three cases with no tubal rupture at laparoscopy (1) Tubal abortion may be a result of extraction of ectopic pregnancy material by tubal peristalsis from the fimbrial end, which was lysed and gotten smaller by the antimetabolic affect of methotrexate. (2) Surgical intervention may be delayed even if the clinical symptoms of tubal rupture had occurred and expectant management with close observation should be a suitable way of follow up for these patients because of tubal abortion probability.

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Ectopic pregnancy is the second major cause of overall maternal mortality and the leading cause during the first trimester.¹ In U.S the rate of ectopic pregnancy has increased from 4.5 per 1000 pregnancies to 19.7 between 1970 and 1992.² Almost all ectopic pregnancies are located in the fallopian tube (97%). In many women a confident diagnosis can now be made before tubal rupture occurs with earlier diagnosis, it has now become apparent that many tubal pregnancies can be followed up with a low chance of sudden hemorrhage. This has resulted in increasing rate of medical therapy use for the treatment of ectopic pregnancy.

Many agents have been employed but methotrexate is the most common medication. This agent can be administered either locally or systemically. Systemic administration can be done as multiple or single dose regimen.^{3,4} Because of high incidence of side effects single dose regimen is being preferred recently.

The criterias for patient selection for methotrexate injection are; hemodynamic stability of the patient, no detectable intrauterine pregnancy, $\leq 4 \text{ cm}$ of ectopic material diameter, no evidence of rupture, hCG (human chorionic gonadotropin) titers less than 10000 IU/L.⁵

We have used single dose methotrexate regimen for three patients who had the inclusion criterias. We have performed laparoscopy for the clinical symptoms of tubal rupture (sudden abdominopelvic pain and ultrasonographically detected fluid accumulation in Douglas pouch) approximately third day following the medication.

Gulhane Military Medical Academy, Department of Obstetrics & Gynecology, Etlik, Ankara, Turkey

Address of Correspondence Murat Dede

GATA

Department of Obstetrics & Gynecology

06018, Etlik, Ankara, Turkey

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Case 1

A 22 years old woman who had 14 days menstrual delay and 2400 IU/L hCG titers and left 3x3 cm juxtauterin mass on transvaginal ultrasonography. The patient had no pregnancy before. 50 mg/m^2 (88 mg total for 1.76 m^2) of methotrexate had been used as intramuscular single dose. hCG titers were 1300 IU/L 24 hours after the injection. Laparoscopy was planned because of sudden inguinal-pelvic pain, approximately 80 ml. of free fluid in Douglas pouch on transvaginal ultrasonography and clinical suspicion of tubal rupture approximately on the third day of injection. On laparoscopic examination there was no tubal damage or sign of rupture and aborted ectopic material was in periovarian space with some hemorrhagic fluid. The case has been thought as tubal abortion. hCG titer was less than 10 IU/L on post injection 15th day.

Case 2

A 26 years old, gravida 2, parity 1 woman who had 10 days menstrual delay, 1600 IU/L hCG titer, left 4x4 cm of juxtauterin mass and no intrauterine gestational sac on transvaginal ultrasonography. 50 mg/m^2 methotrexate (92 mg total for 1.84 m^2) been used as intramuscular single dose. Laparoscopy has been performed 80 hours after the injection because of sudden inguinal-pelvic pain of patient, approximately 50 ml. of free fluid in Douglas pouch on transvaginal ultrasonography and clinical suspicion of tubal rupture. There was no sign of tubal damage. Aborting ectopic material from the left fimbrial end was observed. The hCG titer was 60 IU/L and 10 IU/L eight and fifteenth days after the injection respectively.

Case 3

A 30 years old, gravida two, parity one, 21 days of menstrual deletion, 4400 IU/L of hCG titer, right 4x4 cm of juxtauterin mass on transvaginal ultrasonography and no intrauterine gestational sac.

50 mg/m² (84 mg total for 1.67 m²) of methotrexate had been used as intramuscular single dose. Laparoscopy has been performed 65 hours after the injection for sudden inguinal-pelvic pain of patient, approximately 50 ml. of free fluid in Douglas pouch on transvaginal ultrasonography and clinical suspicion of tubal rupture. There was no sign of tubal damage or rupture but right tuba uterina was distended and hyperemic on ampullary portion. There was minimal hemorrhage from the fimbrial end and aborted material was in Douglas pouch with some hemorrhagic fluid. The case has been accepted as tubal abortion. The post injection hCG titers were 2400 IU/L, 800 IU/L, 60 IU/L, 15 IU/L on days third, fifteenth, twentieth and twenty-ninth respectively.

Discussion

Methotrexate injection for tubal ectopic pregnancy in selected patients has been shown to be an effective alternative to operative laparoscopy in numerous studies.^{6,7} It is an active drug in the first line treatment of cervical metastatic squamous cell carcinoma and gestational trophoblastic disease. The mechanism of action is antagonism of folic acid in DNA and RNA and some protein synthesis pathway.

The clinical observation of tubal abortion was proved in these three cases. The mechanism may be as follows: Gestational trophoblastic tissue may go to lyses and necrosis by anti-metabolic activity of the agent. This affect may get smaller the gestational tissue and peristaltic activity of the tube may cause the abortion of this material from the fimbrial end of the fallopian tube. The sudden pelvic-inguinal pain may be the result of separation of ectopic material from the tubal wall. Lipscomb et al. had also used the "separation pain" definition for pelvic pain after single dose methotrexate therapy for ectopic pregnancy in their study⁸ It should be expected that the abortion procedure may cause sudden or crampy pelvic-inguinal pain.

Sudden pelvic-inguinal pain and free fluid accumulation in pelvis after methotrexate injection in selected patients may be signs of tubal rupture as well as of tubal abortion. Prompt surgical management may be delayed and the probability of tubal abortion should be in mind. Expectant management and close clinical observation may be an alternative follow up way for these patients. The results of new studies which will be done by large series will make clearer of our minds in this area in the future.

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