Local Methotrexate Treatment of Cornual and Cervical Ectopic Pregnancies: Report of Six Cases

Kornual ve Servikal Ektopik Gebeliklerin Lokal Metotreksat ile Tedavisi: Altı Olgunun Sunumu

Abstract

Interstitial (cornual) pregnancy is a rare type of ectopic pregnancy (2-4%) with a high morbidity and mortality rate. The most morbid complication of cornual pregnancy is cornual rupture which may result in severe haemorrhage, hypovolemia and shock. The other rare ectopic pregnancy is seen on the cervix. The incidence of cervical pregnancy has been calculated as between 1 in 1000 or 1 in 18 000 live births or less than 1% of ectopic pregnancies. After final diagnosis for these morbidities, medical or surgical treatment modalities may be preferred. But due to high morbidity and mortality rates of the surgical procedures conservative therapy with methotrexate has been preferred recently. Here in, we present six cases of ectopic pregnancies; five cornual, and one cervical, successfully treated with transvaginal ultrasonography guided local methotrexate injection.

Key Words: Pregnancy, ectopic; methotrexate

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Local pregnancies localised in the interstitial part of fallopian tube which lie within the muscular wall of the uterus are called interstitial (cornual) pregnancies. It is a rare type of ectopic pregnancy (2-4%) with a high mortality rate (2-2.5%). The myometrium of the cornua has a great expansion capacity therefore the symptoms usually occur very late and early diagnosis is usually not possible. The diagnosis usually delays to the 7th-12th weeks of gestation. The most morbid complication of cornual pregnancy is cornual rupture which may result in severe haemorrhage, hypovolemia and shock. Therefore early diagnosis is very important. Differential diagnosis must be done to rule out normal pregnancy with nor-
mal anatomy, normal pregnancy with uterine anomaly; bicornuate or septate uterus and heterotopic pregnancy. The other rare ectopic pregnancy is seen on the cervix. The incidence of cervical pregnancy has been calculated as between 1 in 1000 or 1 in 18 000 live births or less than 1% of ectopic pregnancies. Women with cervical pregnancy generally present with painless first-trimester vaginal bleeding, although they may rarely have cramping pain. A soft cervix that is disproportionately enlarged compared with the uterus, a partially open external os, and abundant hemorrhage on manuplation of the cervix are the clinical signs that suggest cervical pregnancy. Under transvaginal ultrasound examination; the placenta and chorionic sac containing the live pregnancy below the internal os and the dilated cervical canal are seen. Differential diagnosis of cervical pregnancy from cervical abortion must be done. The sliding sign; the sliding of gestational sac of an abortus against the endocervical canal when gentle pressure on the cervix with transvaginal probe is done; can help the differential diagnosis.

After final diagnosis for these morbidities, medical or surgical treatment modalities may be preferred. But due to high morbidity and mortality rates of the surgical procedures conservative therapy with methotrexate has been preferred recently. Methotrexate (MTX) can be given via intravenous route, or injected under ultrasonographic or laparoscopic guidance.

Herein, we present six cases of ectopic pregnancies; five cornual, and one cervical, treated with transvaginal ultrasonography (USG) guided local methotrexate injection.

### CASE REPORTS

#### CASE 1

A 25-year-old woman, gravida 3, para 0, was admitted to the hospital with 8 weeks delay in menstruation and abdominal pain. The uterus was enlarged irregularly, and the βhCG was 20 000 mIU/mL. By the ultrasonographic evaluation, a 3.6 cm large right cornual pregnancy was diagnosed with cardiac activity. To confirm the stretched part of the myometrium and to decide the possibility of direct MTX injection, laparoscopy was done. 50 mg of MTX was injected via laparoscopic route. The level of βhCG went rising up and 48 hours later reached up to 43 800 mIU/mL. By the fact that ultrasonographic evaluation revealed cardiac activity, a second 50 mg of MTX was injected by USG guidance. After an additional 48 hours follow up period the cardiac activity disappeared and the βhCG level fell to normal limits within 27 days. The follow up went on for 7 months and during this period white blood cell counts, liver and renal function tests were stable (Table 1).

#### CASE 2

A 31-year-old woman presented with 7 weeks delay in menstruation, right lower quadrant abdominal pain and vaginal bleeding to our outpatient unit. She previously had 2 term pregnancies and the vital signs were within normal limits. On the laboratory examination serum the βhCG level was 5324 IU/L. The transvaginal USG demonstrated a pregnancy with cardiac activity on the right lateral uterine wall. Fifty miligrams of MTX was locally injected to the embryo with the guidance of transvaginal USG. After 3 weeks follow-up period the serum βhCG levels returned to normal levels and by the ultrasonographic follow up the resolution of the gestational sac was seen (Table 1).

#### CASE 3

A 28-years old patient with gravida 3, para 1 and abortus 1 applied to our outpatient unit with 5 weeks menstrual delay, spotting type of vaginal bleeding, lower abdominal pain and slight pain with cervical movements. The serum hemoglobin level was 12 g/dL, white blood cell count was 15 000/μL, βhCG level was 153 IU/L. On the transvaginal ultrasonographic scan endometrial thickness was 7 mm and there was no echogenic sign in the adnexial region. The serum βhCG levels were studied with 48 hours intervals, but the increase of βhCG levels was not compatible with normal pregnancy. Repeated transvaginal USG revealed an empty uterine cavity but a gestational sac of 13 mm in diameter was detected that was situated in the
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<td>2 early abortion</td>
<td>Amenorrhea, lower abdominal pain</td>
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<td>5324</td>
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<td>28</td>
<td>G3 P1</td>
<td>1 early abortion</td>
<td>Vaginal bleeding, lower abdominal pain</td>
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<td>-</td>
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<td>27</td>
<td>G1 P0</td>
<td>-</td>
<td>Amenorrhea</td>
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<td>-</td>
<td>14 19</td>
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<td>5</td>
<td>44</td>
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<td>5 weeks</td>
<td>Complete resolution</td>
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G: gravidity; P: parity; NSVD: normal spontaneous vaginal delivery; LMP: last menstrual period; MTX: methotrexate.

**TABLE 1:** Characteristics and treatment modalities of five cornual and one cervical pregnancy.

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left cornual region and the βhCG level was 2600 IU/L (Figure 1A). Fifty miligrams of MTX was given into the sac by the guidance of transvaginal USG. During 3 weeks follow up period the serum βhCG levels decreased and on the control transvaginal USG the sac disappeared (Figure 1B) (Table 1).

**CASE 4**
A 27-year-old primigravid woman applied to our clinic 5 weeks of amenorrhea. Serum βhCG level was 1.419 IU/l when the 15 mm gestational sac of pregnancy was seen by transvaginal sonography in the cornual region. Intra-amniotic 50 mg MTX injection under sonographic guidance was performed. After 3 months follow-up complete resolution was seen (Table 1).

**CASE 5**
A 44-year-old woman who had an ectopic pregnancy previously presented with vaginal bleeding and abdominal pain. The serum βhCG level was 1.555 IU/l and 5 weeks of gestational sac on the transvaginal sonography was seen in the left cornual region. Intra-amniotic 50 mg MTX was injected under ultrasound guidance and after 6 weeks follow-up ultrasound view of pregnancy was lost and βhCG titer became negative (Table 1).

**CASE 6**
A 33-year-old, gravida 2, para 2 woman with vaginal bleeding and 5 weeks of amenorrhea applied to our clinic. Serum βhCG level was 332 IU/L on her admission. Follow-up βhCG levels increase up to 2592 IU/L but the increases were less than 60% within 48 hour intervals. On the physical examination cervix was soft and a dilated cervical canal with a pregnancy containing gestational sac of 16 mm diameter was seen on the transvaginal ultrasonography (Figure 2A). Intramuscular 80 mg MTX was injected to the patient. Since βhCG levels still increased up to 6978 IU/L, after intramuscular injection on the fifth day of follow-up 50 mg MTX was given under transvaginal ultrasound guidance. One week after local treatment, on the transvaginal ultrasonography gestational sac disappeared (Figure 2B) and βhCG levels decreased to 3900 IU/L and complete regression of βhCG level to zero was seen 3 weeks after local treatment (Table 1).

**DISCUSSION**
The incidence of the ectopic pregnancy is 1-3% within all pregnancies and 2-4% of all ectopic pregnancies are cornual (intersititial). The diagnosis of the ectopic pregnancy may be difficult which is mostly based on the patient’s history and gynecological examination by which only 50% of all ectopic pregnancies can be diagnosed. Recently, by the help of USG and βhCG the diagnosis can be made earlier but not for all patients. Furthermore, the diagnosis becomes more difficult when the ectopic pregnancy is interstitial type. Ultrasonography may reveal an eccentrically located gestational sac surrounded by a thin layer of myometrium. On the other hand an eccentrically lo-

![Figure 1: A. Before local methotrexate treatment of cornual pregnancy of 13 mm gestational sac. B. After treatment complete resolution of gestational sac.](image-url)
cated normal pregnancy; due to distortion from uterine fibroids, contractions or anomalies, may be confused with a cornual one. A more specific finding is the sign of interstitial line, which represents “an echogenic line that extends into the upper regions of the uterine horn and borders the margin of the intramural gestational sac”. The diagnosis usually delays because of the distensibility of the myometrium at this site and usually the patients apply the clinics with a complaint of amenorrhea, abdominal pain or anormal vaginal bleeding at 7-12 gestational weeks.

With the recent advances in high resolution scans the early diagnosis became easier and more probable. The 4-dimensional ultrasonography reveals more accurate data for the diagnosis and Magnetic Resonance Imaging (MRI) is also used to confirm the diagnosis of an interstitial and cervical pregnancy. MRI is more appropriate to be used in non-urgent cases and for evaluation of cases when ultrasound scans have been inconclusive.

Before 1980’s cornual and cervical pregnancies were usually diagnosed very late and usually hysterectomy was the choice of treatment. Today, to avoid surgical complications and to preserve fertility, various conservative treatments have been defined. Depending on gestational age and the woman’s desire to maintain fertility different treatment modalities are available. The surgical conservative techniques include intracervical balloon tamponade and cervical curettage, cervical cerclage angioembolization of feeding uterine arteries, curettage and local prostaglandin injection, hysteroscopic resection, and bilateral ligation of uterine or hypogastric arteries. Surgery is generally preferred only when chemotherapy fails or in emergency conditions of life-threatening hemorrhage. Non-surgical methods have been developed recently, by local injection of MTX, actinomycin-D, and etoposide. Farabow et al. were the first to describe the use of MTX for treatment of cervical pregnancy in 1983. Methotrexate is an antagonist of folic acid, which participates in DNA synthesis, and it has the capacity to stop the proliferative cell activity. Batioğlu et al. in 1997 first described successful treatment of cornual pregnancy with methotrexate by using transvaginal ultrasonography. Hung et al. in 1998, analyzed some prognostic factors affecting the outcome of conservative MTX treatment and reported that MTX therapy was associated with higher failure rates in the presence of serum βhCG levels more than 10 000 IU/L, gestational age >9 weeks, positive fetal cardiac activity, and a crown-to-rump length more than 10 mm. Çelik et al. in 2008 presented two cases of cervical pregnancies treated by intraamniotic MTX injection. They stated that local MTX treatment was reliable and should be offered but severe vaginal bleeding should be in consideration even during β-hcg levels were decreasing.

In our six patients, we used transvaginal ultrasonography guided MTX injection as a non-inva-
sive and a simple approach. This method has a less morbidity rate and also has least complications like uterine rupture or massive bleeding which is frequently observed by curetage. In our clinic, also a rudimentary horn pregnancy was treated with local methotrexate administration.23

In conclusion, the ultrasound-guided intra-amniotic injection of MTX in the management of rarely seen cornual, cervical and rudimentary horn ectopic pregnancy which are extracavitary but uterine ectopic pregnancies appears to be an effective and safe method; however, therapeutic way preferred depends on the gestational age, des-ire of the patient to preserve fertility, and mostly on hemodynamic stability, therefore the treatment modality must be tailored to the patient.

REFERENCES