

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

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ÖZET Kornual (interstisyel) gebelik ektopik gebeliğin nadir görülen (%2-4), ama yüksek morbidite ve mortalite gösteren bir şeklidir. Kornual gebeliğin en ağır problem oluşturan komplikasyonu, şiddetli kanama, hipovolemi ve şok ile seyredabilen kornual rüptürdür. Bir diğer nadir ektopik gebelik şekli de servikal gebeliktir. İnsidansı 1000 ile 18 000 canlı doğumda 1 olup, ektopik gebeliklerin %1'inden azını oluşturur. Tanının konulmasından sonra, tıbbi veya cerrahi tedavi yöntemleri tercih edilmektedir. Yakın dönemde, cerrahi yöntemlerin yüksek morbidite ve mortalite oranları taşınması yüzünden metotreksat ile konservatif yaklaşımlar tercih edilmektedir. Bu yazıda, beşi kornual, biri servikal olmak üzere transvajinal ultrasonografi eşliğinde lokal metotreksat enjeksiyonu ile başarılı bir şekilde tedavi edilen altı ektopik gebelik olgusu sunulmuştur.

Anahtar Kelimeler: Gebelik, ektopik; metotreksat

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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The 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%).¹ 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-12nd weeks of gestation.² 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.³ 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.^{4,5} 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 manipulation 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.⁶ 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 β hCG 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 β hCG 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 β hCG 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 β hCG level was 5324 IU/L. The transvaginal USG demonstrated a pregnancy with cardiac activity on the right lateral uterine wall. Fifty milligrams of MTX was locally injected to the embryo with the guidance of transvaginal USG. After 3 weeks follow-up period the serum β hCG 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/ μ L, β hCG 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 β hCG levels were studied with 48 hours intervals, but the increase of β hCG 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

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

Case No	Maternal age (years)	Gravidity and parity	Obstetric history	Presenting symptoms	Gestational age (by LMP) at diagnosis	Fetal heart beat	Pretreatment hCG levels (IU/l)	Imaging modality	Management of pregnancy under ultrasound guidance	Repetition of treatment	Length of follow-up	Maternal outcome
1	25	G3 P0	2 early abortion	Amenorrhea, lower abdominal pain	8 weeks	+	20 000	Transvaginal sonography	Intra-amniotic 50 mg MTX injection under laparoscopy guidance	Intra-amniotic 50 mg MTX injection under ultrasound guidance	7 months	Resolution
2	31	G3 P2	2 NSVD	Lower abdominal pain	7 weeks	+	5324	Transvaginal sonography	Intra-amniotic 50 mg MTX injection under ultrasound guidance	-	3 weeks	Complete resolution
3	28	G3 P1	1 early abortion 1 NSVD	Vaginal bleeding, lower abdominal pain	5 weeks	-	2600	Transvaginal sonography	Intra-amniotic 50 mg MTX injection under ultrasound guidance	-	3 weeks	Complete resolution
4	27	G1 P0	-	Amenorrhea	5 weeks	-	1419	Transvaginal sonography	Intra-amniotic 25 mg MTX injection under ultrasound guidance	-	3 months	Complete resolution
5	44	G2 P0	Ectopic pregnancy 1	Vaginal bleeding, abdominal pain	5 weeks	-	1555	Transvaginal sonography	Intra-amniotic 50 mg/kg MTX injection under ultrasound guidance	-	6 weeks	Complete resolution
6	33	-	-	Vaginal bleeding	5 weeks	-	2592	Transvaginal sonography	Intramuscular 80 mg MTX injection	Intra-amniotic 50 mg MTX injection under ultrasound guidance	5 weeks	Complete resolution

G: gravidity; P: parity; NSVD: normal spontaneous vaginal delivery; LMP: last menstrual period; MTX: methotrexate.

left cornual region and the β hCG level was 2600 IU/L (Figure 1A). Fifty milligrams of MTX was given into the sac by the guidance of transvaginal USG. During 3 weeks follow up period the serum β hCG 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 β hCG 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 β hCG 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 β hCG 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 β hCG level was 332 IU/L on her

admission. Follow-up β hCG 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 β hCG 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 β hCG levels decreased to 3900 IU/L and complete regression of β hCG 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 (intersitial). 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 β hCG 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-

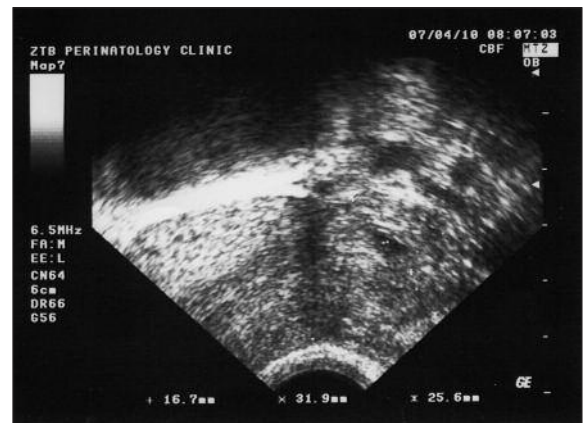
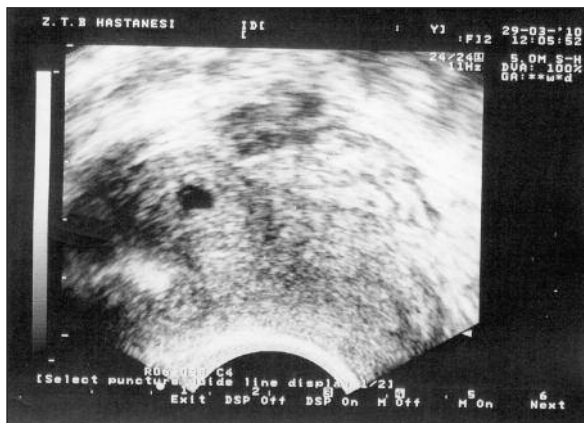


FIGURE 1: A. Before local methotrexate treatment of cornual pregnancy of 13 mm gestational sac, B. After treatment complete resolution of gestational sac.

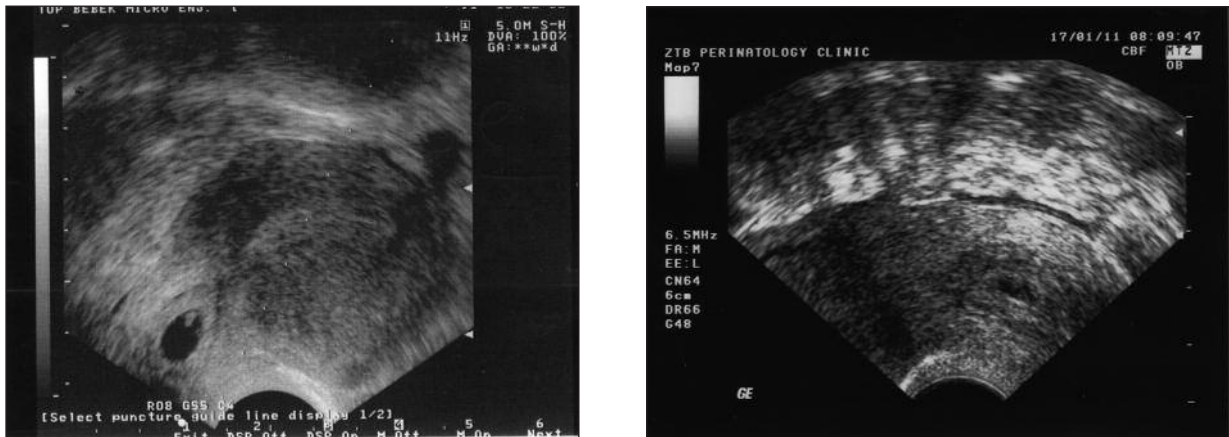


FIGURE 2: A. Before local methotrexate treatment of cervical pregnancy with cardiac activity, B. After treatment complete resolution.

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.^{7,8}

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.⁹⁻¹⁴ 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.¹⁵⁻¹⁷ Farabow et al. were the first to describe the use of MTX for treatment of cervical pregnancy in 1983.¹⁸ Methotrexate is an antagonist of folic acid, which participates in DNA synthesis, and it has the capacity to stop the proliferative cell activity.¹⁹ Batioğlu et al. in 1997 first described successful treatment of cornual pregnancy with methotrexate by using transvaginal ultrasonography.²⁰ 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 β hCG 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.²¹ Çelik et al. in 2008 presented two cases of cervical pregnancies treated by intraamniotic MTX injection.²² 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 curettage. 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, desire of the patient to preserve fertility, and mostly on hemodynamic stability, therefore the treatment modality must be tailored to the patient.

REFERENCES

- Faraj R, Steel M. Management of interstitial (cornual) pregnancy. *Obstet Gynecol* 2007; 9(4):249-55.
- Tulandi T, Al-Jaroudi D. Interstitial pregnancy: results generated from the society of reproductive surgeons registry. *Obstet Gynecol* 2004;103(1):47-50.
- Hammoud AO, Hammoud I, Bujold E, Gonik B, Diamond MP, Johnson SC. The role of sonographic endometrial patterns and endometrial thickness in the differential diagnosis of ectopic pregnancy. *Am J Obstet Gynecol* 2005;192(5):1370-5.
- Parente JT, Chau-su O, Levy J, Legatt E. Cervical pregnancy analysis. *Obstet Gynecol* 1983;62(1):79-82.
- Marcovici I, Rosenzweig BA, Brill AI, Khan M, Scommegna A. Cervical pregnancy. *Obstet Gynecol Surv* 1994;49(1):49-55.
- Timor-Tritsch IE, Monteagudo A, Mandeville EO, Peisner DB, Anaya GP, Pirrone EC. Successful management of viable cervical pregnancy by local injection of methotrexate guided by transvaginal ultrasonography. *Am J Obstet Gynecol* 1994;170(3):737-9.
- Filhastre M, Dechaud H, Lesnik A, Taourel P. Interstitial pregnancy: role of MRI. *Eur Radiol* 2005;15(1):93-5.
- Bader-Armstrong B, Shah Y, Rubens D. Use of ultrasound and magnetic resonance imaging in the diagnosis of cervical pregnancy. *J Clin Ultrasound* 1989;17(4):283-6.
- Nolan TE, Chandler PE, Hess LW, Morrison JC. Cervical pregnancy managed without hysterectomy. A case report. *J Reprod Med* 1989; 34(3):241-3.
- Bachus KE, Stone D, Suh B, Thickman D. Conservative management of cervical pregnancy with subsequent fertility. *Am J Obstet Gynecol* 1990;162(2):450-1.
- Ryu KY, Kim SR, Cho SH, Song SY. Preoperative uterine artery embolization and evacuation in the management of cervical pregnancy. Report of two cases. *J Korean Med Sci* 2001;16(6):801-4.
- Spitzer D, Steiner H, Graf A, Zajc M, Staudach A. Conservative treatment of cervical pregnancy by curettage and local prostaglandin injection. *Hum Reprod* 1997;12(4):860-6.
- Ash S, Farrell SA. Hysteroscopic resection of a cervical ectopic pregnancy. *Fertil Steril* 1996;66(5):842-4.
- Lin H, Kung FT. Combination of laparoscopic bilateral uterine artery ligation and intraamniotic methotrexate injection for conservative management of cervical pregnancy. *J Am Assoc Gynecol Laparosc* 2003;10(2):215-8.
- Dotters DJ, Katz VL, Kuller JA, McCoy MC. Successful treatment of a cervical pregnancy with a single low dose methotrexate regimen. *Eur J Obstet Gynecol Reprod Biol* 1995;60(2): 187-9.
- Brand E, Gibbs RS, Davidson SA. Advanced cervical pregnancy treated with actinomycin-D. *Br J Obstet Gynecol* 1993;100(5):491-2.
- Segna RA, Mitchell DR, Misas JE. Successful treatment of cervical pregnancy with oral etoposide. *Obstet Gynecol* 1990;76(5 Pt 2):945-7.
- Farabow WS, Fulton JW, Fletcher V, Velat CA, White JT. Cervical pregnancy treated with methotrexate. *N C Med J* 1983;44(3):91-3.
- Fernandez H, Yves Vincent SC, Panthier S, Audibert F, Frydman R. Randomized trial of conservative laparoscopic treatment and methotrexate administration in ectopic pregnancy and subsequent fertility. *Hum Reprod* 1998; 13(11):3239-43.
- Atıoğlu S, Haberal A, Yeşilyurt H, Ekici E. Successful treatment of cornual pregnancy by local injection of methotrexate under laparoscopic and transvaginal ultrasonographic guidance. *Gynecol Obstet Invest* 1997; 44(1):64-6.
- Hung TH, Shau WY, Hsieh TT, Hsu JJ, Soong YK, Jeng CJ. Prognostic factors for an unsatisfactory primary methotrexate treatment of cervical pregnancy: a quantitative review. *Hum Reprod* 1998;13(9):2636-42.
- Çelik H, Gürateş B, Artaş Z, Deniz R, Artaş H. [The conservative treatment of cervical ectopic pregnancy with methotrexate: presentation of the two cases]. *Türkiye Klinikleri J Gynecol Obst* 2008;18(3):202-6.
- Hamdemir Kilic S, Aral AM, Batioglu S. An early diagnosis and successful local medical treatment of a rudimentary uterine horn pregnancy: a case report. *Arch Gynecol Obstet* 2007;275(4):297-8.