SURGICAL TREATMENT OF CORNUAL PREGNANCY AFTER PREVIOUSLY ONE TREATED BY METHOTREXATE: CASE REPORT AND LITERATURE REVIEW

KIRUŠKO LIJEČENJE KORNUALNE TRUDNOĆE NAKON PRETHODNE LIJEČENJE METOTREXATOM: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Key words: recurrent cornual pregnancy, interstitial pregnancy, methotrexate, laparoscopy

Summary. Cornual or interstitial pregnancy is a rare form of ectopic pregnancy with a significant mortality rate. The report concerns a recurrent spontaneous cornual pregnancy two years after a cornual pregnancy diagnosed as missed abortion which was successfully treated by the systemic application of methotrexate (MTX). After a lack of success by MTX therapy, recurrent cornal pregnancy was successfully treated laparoscopically. Although conservative medical and surgical methods of management are showing good outcomes, these methods do not protect against recurrence. Conservative medicamentous therapy with parenterally applied methotrexate in cases of cornual pregnancy with early diagnosis and nonviable fetus, provides the possibility of successful treatment and outcome. In cases with viable fetus or unsuccessful treatment with methotrexate, laparoscopic removal of cornual pregnancy is the therapy of choice.

Case report

A 30-year old gravida 5 para 1 was admitted to the Department with a $β$-human chorionic gonadotropin ($β$-HCG) values of 12 937 IU/L, amenorrhoea of 7 weeks and cornual pregnancy in the right cornus diagnosed by ultrasound with positive fetal heart rates (viable fetus). She was haemodynamically stable with no bleeding or abdominal pain.

We present a case of a recurrent cornual ectopic pregnancy treated laparoscopically, after the previous one has been successfully treated by systemic methotrexate therapy.

Introduction

Interstitial or cornual pregnancy is an uncommon form of ectopic pregnancy occurring once in every 2500–5000 pregnancies and represents 2–4% of all ectopic pregnancies. Maternal mortality in case of cornual rupture is described to be 2–2.5% and rates for 20% of all deaths due to ectopic pregnancy.

Some authors differentiate interstitial, cornual and angular pregnancy, but this has not been accepted by majority of clinicians yet. An angular pregnancy refers to the viable intrauterine pregnancy that is implanted in one of the lateral angles of the uterine cavity, medial to the uterotubal junction. On the other hand, interstitial pregnancy appears laterally to the round ligament. Cornual pregnancy refers to pregnancy in a horn of a bicornuate uterus.

Historically, cornual pregnancies have been treated by laparotomy with hysterectomy or cornual resection. In the last decades, however, several conservative techniques have been introduced: expectant follow-up with regular sonography, local or systemic use of methotrexate, hysteroscopic removal and laparoscopic resection.

We present a case of a recurrent cornual ectopic pregnancy treated laparoscopically, after the previous one has been successfully treated by systemic methotrexate therapy.

Previous pregnancy was managed 2 years before at another clinic. As admitted and initially thought to be an intrauterine pregnancy, missed abortion was diagnosed, and curettage was performed. Histological anal-
ysis showed no products of conception. By repeated transvaginal ultrasound a missed abortion in the right cornus of the uterus was seen with β-HCG values of over 44,720 IU/L. According to these findings, a medical management of ectopic pregnancy was counselled. The patient received 50 mgs of methotrexate (MTX) given by intramuscular injection on the 2nd day of admission. After a slight initial rise in the β-HCG values (45,850 IU/L) at the 4th day after admittance; 7 days after the first dose and an additional 50 mgs of methotrexate given on the 15th day, the serum β-HCG values started to decline gradually (21st day 19,350 IU/L, 25th day 8,320 IU/L and 36th day 1,880 IU/L). The patient was discharged with β-HCG values of 5626 IU/L (29th day) and was monitored until β-HCG values became undetectable.

Due to the recurrent cornual pregnancy in the same right cornus, this actual pregnancy, after consulting the patient, was also initially treated conservatively with 50 mgs of methotrexate (MTX) given by intramuscular injection (1st day, and additionally 6th day the same dose). The concentration of β-HCG at the 1st day of admittance was 12,937 IU/L. Since the initial dose together with additional dose after 6 days did not give satisfactory results with even higher β-HCG values and fetal heart rates still positive, the laparoscopy hysteroscopy were performed on the 9th day of admittance.

Hysteroscopy showed an empty uterine cavity with both tubal ostia without any abnormalities.

The initial ultrasound diagnosis was confirmed by laparoscopy. The described ectopic pregnancy was present in the right cornus of the uterus. An incision was made in the area of the right cornus and the products of conception were removed; thereafter the electrocoagulation was performed for haemostasis. The ectopic pregnancy sac was extruded during the procedure and sent for histological analysis which confirmed products of conception. A right side salpingectomy in an effort to reduce the chance of repeating cornual pregnancy on the same side was performed thereafter. Patient recovered well with β-HCG values of 2,201 IU/L on the 4th post-operative day and falling next values. After being discharged from the hospital, her β-HCG values were monitored until negativization.

Discussion

Cornual or interstitial pregnancy poses a significant diagnostic and therapeutic challenge despite its rarity. It carries a higher maternal mortality rate than ampullar ectopic pregnancy. Cornual pregnancy refers to pregnancies where the conception implants into the proximal portion of the Fallopian tube, which is within the muscular wall of the uterus. Cornual ectopic pregnancies account for 1 in 2,500–5,000 live births and 2–6% of all ectopic pregnancies. Although they carry a significant mortality rate of 2–2.5% and account for 20% of all deaths due to ectopic pregnancies, the incidence of recurrent cornual pregnancy is not known.

Clinical risk factors are as for other types of ectopic pregnancies. Namely, ipsilateral salpingectomy, previous ectopic pregnancy, in vitro fertilization, pelvic inflammatory disease (PID), previous pelvic surgery specially corrective surgery of the Fallopian tubes, congenital uterine anomalies and uterine fibroids are predisposing factors for interstitial pregnancy.

In a series of 32 interstitial pregnancies, the most common risk factors were tubal damage from previous ectopic pregnancy (40.6%), previous ipsilateral or bilateral salpingectomy (37.5%), conception after in vitro fertilization (34.4%) and history of sexually transmitted disease (25.0%).

In another series of 27 patients with interstitial pregnancy the 54% of the patients had a history of salpingectomy or tubal ligation, 54% had a previous ectopic pregnancy, 29.7% had had in vitro fertilization and only 12.5% had a history of pelvic inflammatory disease.

Tubal pathology is often the primary factor blamed for recurrence. Other factors such as assisted conception and the non-invasive management of cornual pregnancies have been shown to contribute to a higher risk of recurrence of cornual pregnancies. Ipsilateral tubal occlusion with the Filshie clip in cases of recurrent cornual pregnancy with a normal looking contralateral tube is a justified attempt to reduce the risk of recurrent cornual pregnancy, although this may not completely prevent recurrence due to zygote transmigration but will definitely reduce it. Regarding assisted conception, an incidence of ectopic pregnancy following IVF-embryo transfer in women with damaged Fallopian tubes is higher than that following spontaneous conception.

The early diagnosis of cornual ectopic pregnancy is an essential problem. With recent advances an interstitial pregnancy is diagnosed at gestational age of 6.9–8.2 weeks. The diagnosis can be made by ultrasound (TVUS – high resolution transvaginal ultrasonography) using the following criteria: a) an empty uterus, b) gestational sac seen separately and less than 1 cm away from the lateral-most edge of the uterine cavity and c) thin myometrium surrounding the sac (less than 5 mm). In addition, ultrasonographers can use the ‘interstitial line sign’ that has a sensitivity of 80% and a specificity of 98%. On ultrasound this is demonstrated as a thin echogenic line that extends directly up to the centre of the interstitial gestational sac. The most common symptoms of interstitial pregnancy are abdominal pain and vaginal bleeding in the first trimester of pregnancy. A study from 2007 has shown that of 27 patients at a mean gestational age of 8.2±2 weeks, only 22.2% presented with ruptured interstitial pregnancy and hemorrhagic shock, while 48% presented with abdominal pain, 29% presented with vaginal bleeding and 33.3% were asymptomatic at the time of diagnosis.

Management of cornual ectopic pregnancy still represents a challenge. Studies using medical management with methotrexate have reported failure rates approach-
ing 35% while various surgical modalities have demonstrated better success rates (72–95%).

Although the traditional method of managing cornual ectopic pregnancies has been by cornual resection, early diagnosis by ultrasound has meant greater widespread use of relatively conservative methods of surgical and medical management. The study of Canis et al. showed a 91% success rate in treating interstitial pregnancies using one-dose intravenous methotrexate plus folic acid with negligible side effects. A randomised controlled trial on using a combination of mifepristone and methotrexate on unruptured tubal ectopic pregnancies found faster resolution of the ectopic pregnancy with the combination treatment. Systemic methotrexate is not without risks. In addition to its side effects, there remains a risk of rupture during treatment and close monitoring of serum β-hCGs is required. Other forms of medical management are available including local injection of methotrexate, potassium chloride or prostangladins under ultrasound, hysteroscopic or laparoscopic guidance.

Various conservative surgical methods have been reported in the literature, i.e. laparoscopic cornual resection or laparoscopic cornuostomy. Radical operations such as hysterectomy are necessary when hemostasis cannot be achieved because substantial hemorrhage can be life-threatening. One study reports the classical laparoscopic method of incising the cornual area after a transparietal xylocaine-adrenaline injection, draining the contents and suturing the area. However, they also used a post-operative systemic methotrexate injection.

Another study described the vasopressin electric cauterisation method. However, the recommendation is that following laparoscopic management in the following pregnancies the patients will require elective caesarean section.

Endoloop technique as described is a simple, safe, effective and nearly bloodless technique for the treatment of selected cases of cornual pregnancy. It is most frequently used in cases of interstitial heterotopic pregnancies because it offers a good prognosis for the ongoing intrauterine pregnancy. Cornual closure is ended simultaneously with the removal of the conception by progressive tightening of the applied endoloop. This technique offers bleeding control during incision of the cornual area and both removal of the conceptus and effective closure of the uterine wall. However, it can only be used in those cases where the cornual pregnancy is slightly elevated or pedunculated from the underlying myometrium. A disadvantage of these conservative surgical techniques is that the cornual area might become dehiscent. Therefore, the pregnancy is accessible vaginally, that is very rare. Transcervical suction curettage is appropriate only under a restricted set of circumstances. The pregnancy must be situated in the proximal portion of the interstitium and preferably there should be a dilated proximal tubal ostium so that it is accessible vaginally. Laparoscopy-guided suction curettage of a cornual ectopic pregnancy in a bicornuate uterus was reported in 2008.

If cornual ectopic pregnancy is diagnosed enough early, it is possible to avoid surgical treatment in most cases. Selective uterine artery embolization has been used after systemic MTX or after the failure of this medical treatment. The authors recommended its use in selected cases of early cornual pregnancy and it could reduce the haemorrhagic risk.

Ipsilateral tubal occlusion with the Filshie clip in cases of recurrent cornual pregnancy with a normal looking contralateral tube is a justified attempt to reduce the risk of recurrent cornual pregnancy, although this may not completely prevent recurrence due to zygote transmigration but will definitely reduce it.

All of these methods offer no real protection against recurrent cornual pregnancies and have implications for future pregnancies. Regardless of this fact, methotrexate (MTX) is considered to be a safe and effective treatment for cornual pregnancy and surgery can be often avoided, as was the case with our initial cornual pregnancy with non-viable fetus. Early recognition of the cornual pregnancy with transvaginal ultrasound at haemodynamic stability and non-viable fetus with no signs of rupture are essential for medical management. The risk of rupture during treatment should always be considered and frequent monitoring of serum β-hCG values is required. Follow up of hCG trends or the clinical symptoms predict the need of additional doses of MTX. A study of Jermy et al. reported the successful treatment of unruptured interstitial pregnancies with systemic methotrexate (MTX) in 16 of 17 patients (94%). All patients with an initial β-hCG level of < 5000 IU/L were treated successfully with a single intramuscular dose of 50 mg/m² body surface area.

We believe the systemic methotrexate is the therapy of choice in cornual pregnancy treatment when laparoscopy is not essential for diagnosis and with non-viable fetus in haemodinamically stable patient. In cases of failure of this method, laparoscopic removal of cornual pregnancy should be performed. When the use of medical management with MTX was proven to be unsuccessful, like in the case of our recurrent cornual pregnancy in the right cornus, surgical laparoscopy was successfully performed. As a reminder we would to stress out that this was a case of a conservative attempt of treatment of a viable cornual pregnancy on patient’s desire who refused laparoscopy as a therapy of choice.

Despite the higher β-hCG values in patient’s first cornual pregnancy, treatment with MTX was successful unlike her recurrent cornual pregnancy with much lower
hCG values. We believe that this is due to the fact that in initial pregnancy we had a case of a missed abortion with negative fetal heart rates while in her recurrent pregnancy we had a viable fetus.

**Conclusion**

Recurrence of interstitial pregnancy is undoubtedly rare. It is important in cases of cornual ectopic pregnancies, since the most conservative surgical and medical management techniques do not remove the interstitial portion of Fallopian tube, that we consider responsible for persistent trophoblastic tissue and recurrence in future pregnancies. Medical management has proven to be more beneficial in the cases of non viable fetuses with a higher chance of successful treatment and outcome. In patients with viable fetus, in our opinion, the therapy of choice should be laparoscopic removal of cornual pregnancy, especially in recurrent cornual pregnancy cases.

**References**


Diseminirana peritonealna leiomiomatoza
– PRIKAZ SLUČAJA

LEIOMYOMATOSIS PERITONEALIS DISSEMINATA – A CASE REPORT

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Prikaz bolesnice

**SUMMARY.** Leiomyomatosis peritonealis disseminata (LPD) is a rare but well documented disorder mainly found in women in reproductive period. It is characterized by multiple small nodules on the peritoneal surface, mimicking a malignant process, but demonstrates benign histologic features. It is usually an incidental finding during procedures such as laparoscopy, cesarean section, laparotomy, tubal ligation etc. Etiology is unknown but LPD seems to be a multifactorial disease with a genetec or hormonal component (high levels of estrogen and progesterone) leading to metaplasia of peritoneal mesenchymal cells. There is evidence to suggest that LPD is a product of a hormonal imbalance. When LPD occurs during pregnancy or during the use of birth control pills (contraceptive pills), it may regress spontaneously after delivery or discontinuation of the use of the pills. In this paper we report a case of LPD in a pregnant woman, who has been using birth control pills for three years between two pregnancies.

**Uvod**

Diseminirana peritonealna leiomiomatoza (DPL) je prvi put opisana 1952. (Wilson i Pale). Do sada je opisano oko 150 slučajeva. Radi se o multiplim malim tumorima građenim od glatkog mišića, koji su razasuti po potrudnici. Najčešće se radi o slučajnom nalazu tijekom operacije (carski rez, laparoskopija, laparotomija) te je moguće da je bolest izazvao stajalište sa karcinomatozom peritoneja, jer je makroskopski izgled sličan. Ovo benigno stanje često se zamjenjuje sa karcinomatozom potrudnici, jer se pojavljuju mnogo ~vori}a razli~ite veli~ine, od par milimetara do oko 2 cm u promjeru (slika 1.) Mnogobrojni ~vori}i, uglavnom manji, u prosjeku 3–4 mm, nalazili su se po serozi uterusa i po pari~telnoj potrudnici u tijeku ~vori}a. U većini opisanih slu~aja obilježavale su bolesnice reprodutivne dobi, većina je povezana s trudno{a.

**Prikaz slučaja**

Trudnica P.R., 33 godine, primljena je na naš odjel zbog planiranog elektivnog carskog reza u 39. tjednu druge trudno{e. Ova doba je opisano 150 slučajeva. Radi se o multiplim malim tumorima građenim od glatkog mišića, koji su razasuti po potrudnici. Najčešće se radi o slučajnom nalazu tijekom operacije (carski rez, laparoskopija, laparotomija) te je moguće da je bolest izazvao stajalište sa karcinomatozom peritoneja, jer je makroskopski izgled sličan. U većini opisanih slučaja obilježavale su bolesnice reprodutivne dobi, većina je povezana s trudno{a. Neke bolesnice koje nisu bile gravidne, uzimale su OHK.1

Druga trudno{a je protekla uredno. Kod prijama (u srpnju 2010.), trudnica je afebrilna (37°C), tlak je 125/75 mm Hg. Preoperacijska obrada pokazuje uredne bioke mijske parametre. Opstetri~ki i UZV nalaz odgovaraju termi~skoj trudno{i. Drugi dan po prijemu u~injena je biopsija ex tempore, koja je pokazala da se radi o benignoj promjeni. Uzeti su i uzorci tkiva tumora za trajnu patohistolo{ku analizu. Postoperacijski tijek je protekao uredno. Sedmog dana je otpu{tena kao zdrava babi{nica. Prvi UZV pregled je obavljen tri mjeseca nakon poroda i pokazao je glatku povr{inu uterusa bez prisustva bilo kakvih ~vori}a. Bolesnica je pregledana jo{ tri puta UZV-om te nisu na|ene nikakve tvobe na uterusu ni drugdje.

**Ključne riječi:** leiomiomatoza peritonelana, trudno{a

**S}A}ZETAK.** Diseminirana peritonealna leiomiomatoza (DPL) je rijedak klini~ki entitet, karakteriziran pojavom multiplih miomatoznih ~vori}a, razasutih po potrudnici. Makroskopskim izgledom opona{a karcinomatozu potrudnici, ali se radi o benignoj bolesti. Bolest je rijetka, (u literaturi se navodi 100–150 do sada opisanih slu~ajeva), ali dobro dokumentirana. Postoji mogu}nost da je i ~e{}a, jer je većina bolesnica bez simptoma. Bolest se naj~e{}e na|e slu~ajno, u sklopu kirur{kih zahvata (laparoskopija ili laparotomija) indicirani drugim bolestima. Pojavljuje se uglavnom u ~ena reproducitivne dobi. Pretpostavlja se da tumori nastaju metapazijom submezotelnih multipotentnih mezenhimalnih stanica. Ako se pojavi tijekom trudno{e ili uzimanja oralnih kontraceptiva (OHK), regredira spontano nakon poroda ili prestanka uzimanja OHK. Ovde prikazujemo slu~aj DPL-a koji je na|en slu~ajno pri carskom rezu u bolesnica koja je tri godine uzimala OHK.