



## Multidose methotrexate treatment of cornual pregnancy after in vitro fertilization: Two case reports

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### ABSTRACT

**Background:** An ectopic pregnancy, when the gestational sac is implanted outside of the uterine cavity, can be life-threatening. A cornual pregnancy is the most dangerous type of ectopic pregnancy since it can be misdiagnosed easily and has high mortality rate. It is diagnosed when the implantation site is at the junction between the fallopian tube and the uterus. For a successful outcome, early diagnosis and management are critical. The traditional management is surgical, involving cornual resection or hysterectomy, which, however, affects fertility. Thus, conservative management involving administration of methotrexate should always be considered. **Case presentation:** The article describes two women in their early forties with no previous children (G1, P0) and diagnosed with a cornual pregnancy at 7 and 8 weeks of gestation following in vitro fertilization. Given their hemodynamic stability and their desire to conserve fertility they were treated conservatively. The two patients had similar ultrasound findings and blood results. The main difference was the presence of an embryonic heart beat in one case. Successful management was accomplished with multidose methotrexate and leucovorin during hospitalization for 8 days and close monitoring for the next 30 days as outpatients. In addition, the second woman was given a transvaginal injection of potassium chloride (KCL) to stop embryonic cardiac activity. **Conclusion:** Conservative management of cornual pregnancies applying multidose therapy of methotrexate and leucovorin is a safe treatment when patients are asymptomatic and preserves fertility.

### 1. Introduction

A cornual pregnancy is diagnosed when the implantation takes place at the uterine part of the fallopian tube or in the cavity of a rudimentary uterine horn which may or not be communicating with the uterine cavity [1,2]. It has a mortality rate that is 6–7 times higher than all ectopic pregnancies combined. This is due to the zone of implantation growing and secondary rupturing at a later gestational age, resulting in severe hemodynamic compromise. Fortunately, it is a rare phenomenon, accounting for only 2–4% of all ectopic pregnancies [3,4]. The clinical symptoms of a cornual pregnancy, as with every case of ectopic pregnancy, depend on whether it has been ruptured or not. When it is ruptured, intraperitoneal hemorrhage produces significant abdominal discomfort, as well as varying degrees of hemodynamic instability. Unruptured cornual pregnancy, on the other hand, is often accompanied by moderate pelvic pain and vaginal bleeding, or is asymptomatic [5].

Ultrasonography or laparotomy are used to diagnose a cornual ectopic pregnancy. The presence of an implanted blastocyst within the gestational sac in the uterine cornua, between the proximal part of the fallopian tube and the uterine musculature, covered by a thin myometrial layer with enhanced vascularity, is a common ultrasonography finding [6].

Risk factors include history of ipsilateral salpingectomy, a previous ectopic pregnancy, pelvic inflammatory disease and use of assisted reproductive techniques (ART) [7,8]. However, no risk factors are present in 50% of all women diagnosed with a cornual pregnancy [9]. The symptoms of a cornual pregnancy appear later compared to an ectopic pregnancy, leading to higher probability of rupture [10]. The mortality rate is significantly high (2.2%–2.5%) since a rupture is associated with massive intraperitoneal bleeding and hemorrhagic shock, requiring urgent management [11]. There are two ways to manage cornual gestation: a surgical approach or medical treatment.

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Traditionally, laparotomy was performed; however, following the introduction and refinement of laparoscopic surgery it is now possible to manage these cases without a laparotomy, even in ruptured cases [12]. It should be emphasized, however, that in some cases a hysterectomy may be the only solution [2]. Regarding non-surgical management, systemic methotrexate administration, or ultrasound-guided or laparoscopic-guided methotrexate injection, are safe and highly effective treatments for cornual pregnancy and avoid the need for surgery [13]. Methotrexate (MTX) can be administered via a single, double or multiple injections. Multiple-dose MTX treatment of cornual ectopic pregnancies appears to be a safe and effective method, but the success of the therapy depends strongly on body mass index, MTX dose, number of MTX injections and a decrease in  $\beta$ -hCG levels [14].

## 2. Case Presentation

In this paper, 2 similar cases of cornual pregnancy are reported. The first case involves a 40-year-old Caucasian pregnant woman (G1, P0) who presented at the outpatient clinic for a routine ultrasound scan 3 weeks after a positive pregnancy test following in vitro fertilization (IVF). She had been trying to get pregnant for 6 years and this was her fourth IVF attempt. The woman had no clinical symptoms and her ultrasound scan revealed a gestational sac at the right cornus surrounded by myometrium, with no presence of cardiac activity (Fig. 1). Her laboratory blood results were within normal limits: WBC 6.670/ $\mu$ L, Hb 14,4 g/dL,  $\beta$ -hCG 4032 IU/L.

The diagnosis was discussed with the patient and the treatment choices were explained in detail. She was informed that laparoscopic excision would be the safest method but she was also warned about the potential impact of the operation on her fertility. She was reluctant to risk her fertility and thus preferred a conservative approach. She met all the criteria for conservative management, and thus the regime of methotrexate (MTX) and folinic acid was initiated. The woman was also consented for a surgical approach in case of a rupture during the treatment.

On day 1 of hospitalization, she was administered 100 mg MTX iv in 200 mL normal saline 0.9% over the course of two hours, followed by folinic acid 10 mg im the next day. On day 3, blood results were as follows: WBC 4.150/ $\mu$ L, Hb 14.2 g/dL,  $\beta$ -hCG 4.165 IU/L. According to the hospital guidelines [1–17], since  $\beta$ -hCG serum levels had not declined by more than 15%, the treatment continued in the same way. The patient received three more doses of MTX 100 mg on days 3, 5 and 7 and every dose was followed by administration of folinic acid 10 mg, on

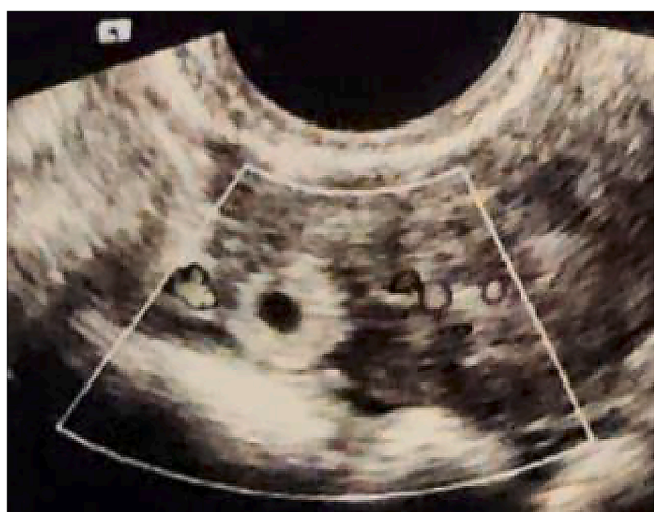


Fig. 1. Transvaginal ultrasound highlights the cornual pregnancy on the day the woman presented for the first time at the emergency department of the hospital.

days 4, 6 and 8. The woman was under close monitoring via ultrasound scans and blood tests every second day. On day 7, her  $\beta$ -hCG serum levels started to decline for first time and the woman was able to leave the hospital. She had a blood test every 4 days to monitor the  $\beta$ -hCG level, which was decreasing, until it went below 5 IU/L 35 days since initiation of treatment. On that day the woman returned to the hospital for the last follow-up ultrasound and blood test. Her uterus appeared normal, with no retained products of conception.

The second patient was a 43-year-old Caucasian woman (G1, P0) who presented at the early pregnancy assessment unit complaining about brown watery discharge and mild abdominal pain in her lower abdomen, on the 8th week of gestation after her fifth IVF attempt. She had been trying to conceive for 6 years.

Initial vital signs were as follows: temperature 36.8 °C, pulse 79 per minute, blood pressure 116/78 mmHg, oxygen saturation 100%. After clinical examination, transvaginal ultrasound was performed and showed a cornual pregnancy at the left cornus with a crown-rump length of 9.9 mm, a gestational sac measuring 11.8 mm, a yolk sac measuring 5.2 mm, and an embryonic heart rate of 125 beats per minute. Her blood results were within normal limits: WBC 8.552/ $\mu$ L, Hb 13,6 g/dL,  $\beta$ -hCG 5560 IU/L.

Following discussion with the patient regarding the findings and the spectrum of treatments available, she opted for conservative management with the multidose protocol of MTX and folinic acid similar to the previous case. However, because of the presence of embryonic heart beat, 0.5 cc KCL 10% was also injected to the embryonic heart by ultrasound guidance.

Subsequently, the same management as described for the first case was performed. The woman remained hospitalized for 8 days, since  $\beta$ -hCG, measured every second day, showed no decline >15%. On day 5, her  $\beta$ -hCG serum level was about the same compared to day 3, but it started to decline on day 7 of hospitalization. The patient left the hospital on day 8 after the last injection of folinic acid, against medical advice. Her  $\beta$ -hCG serum levels, measured every 4 days, decreased steadily. On day 40 after treatment initiation, she returned to the hospital for the last ultrasound and blood test. There were no retained products of conception and  $\beta$ -hCG was 3.56 IU/L.

## 3. Discussion

Certain conditions must be satisfied for medical treatment of cornual pregnancy with MTX. Because MTX affects rapidly growing tissues, chronic liver illness, blood dyscrasias, pulmonary disease, gastric ulcer, and immunodeficiency are absolute contraindications. Furthermore, MTX should not be given to individuals who have a known sensitivity to the medication or who are lactating. Unruptured masses more than 3.5 cm in diameter and  $\beta$ -hCG levels greater than 6.000–15.000mIU/mL are relative contraindications, and physicians should weigh the risks and benefits before administering MTX to these patients [15]. Embryonic cardiac activity is also a relative contraindication for MTX administration; however, when combined with KCL injection it appears to be safe and successful [16]. When the conditions for methotrexate use are met, the important advantage of such an approach is the maintenance of fertility. In the literature, different doses have been reported for MTX injection: 12.5 mg, 25 mg, 50 mg and 100 mg [10,17]. Different publications describe different procedures, such as single or multiple MTX doses, and both appear to be safe and effective, as there have been several cases of intrauterine pregnancy following various methotrexate treatment schemes [14].

## 4. Conclusion

Although uncommon in the general population, ectopic pregnancy and - in our cases - cornual ectopic pregnancy are much more common among women who have used assisted reproductive techniques. The traditional treatment is operation by cornual resection, but conservative

management should be considered wherever possible since it is safe and effective, and allows fertility to be preserved. However, close monitoring is recommended since an operation is unavoidable if the woman becomes hemodynamically unstable.

Regarding our cases, multidose treatment with the combination of MTX and folic acid achieved the successful management of the cornual pregnancy, even in the second case - where there was embryonic heart beat and the patient's  $\beta$ -hCG level was more over 5.000 IU/L - with no impact on fertility.

#### Contributors

All authors have made contributions to the conception and design of the study, drafting and revising the article. All authors were involved in the patients' care. All authors approved the final version.

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#### Patient consent

Obtained.

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#### Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

#### References

- [1] N. Malhorta, J. Malhorta, R. Saxena, Bora N. Malhorta, Jeffcoate's Principles of Gynaecology, 9th ed., Jaypee Brothers, New Delhi, 2019.
- [2] R. Rastogi, M. Gl, N. Rastogi, V. Rastogi, Interstitial ectopic pregnancy: a rare and difficult clinicsonographic diagnosis, *J. Hum. Reprod. Sci.* 1 (2) (2008) 81–82.
- [3] I. Ulu, S.B. Turkmen, G. Kiran, A case of a ruptured cornual in vitro fertilization pregnancy, *J. Women's Health Care* 5 (2016) 5–329.
- [4] E. Bonfante Ramfrez, R. Bolaños Ancona, L. Juárez García, L.S. Pereira, García-Benitez C. Quesnel, Embarazo cornual, *Ginecol. Obstet. Mex.* 66 (1998) 81–83.
- [5] A. Galani, A. Zikopoulos, E. Moulis, M. Paschopoulos, K. Zikopoulos, Successful conservative medical management of an interstitial ectopic pregnancy at 10 weeks of gestation: a case report, *Case Rep Womens Health.* 26 (29) (2020 Dec) e00284.
- [6] E.P. Lin, S. Bhatt, V.S. Dogra, Diagnostic clues to ectopic pregnancy, *Radiographics.* 28 (6) (2008) 1661–1671.
- [7] A. Fabre-Gray, M. Read, P. Wardle, M. James, Recurrent cornual pregnancy, successfully treated with methotrexate, following a ruptured pregnancy in the contralateral cornu, *J. Obstet. Gynaecol.* 34 (2014) 85–100.
- [8] S. Rathod, S.K. Samal, A true cornual pregnancy with placenta percreta resulting in a viable fetus, *Int. J. Appl. Basic Med. Res.* 5 (3) (2015) 203–205.
- [9] H. Zamané, et al., Bilateral tubal pregnancy without known risk factor, *Case Rep. Obstet. Gynecol.* 2017 (2017) 4356036.
- [10] R. Ross, S.R. Lindheim, D.L. Olive, E.A. Pritts, Cornual gestation: a systematic literature review and two case reports of a novel treatment regimen, *J. Minim. Invasive Gynecol.* 13 (1) (2006) 74–78.
- [11] B.M. Parker, A.K. Gupta, A. Lymperopoulos, J. Parker, Methotrexate for cornual ectopic pregnancy, *Cureus* 12 (8) (2020), e9642.
- [12] M.S. Walid, R.L. Heaton, Diagnosis and laparoscopic treatment of cornual ectopic pregnancy, *Ger. Med. Sci.* 8 (2010) Doc16.
- [13] S. Rathod, S.K. Samal, A true cornual pregnancy with placenta percreta resulting in a viable fetus, *Int. J. Appl. Basic Med. Res.* 5 (3) (2015) 203–205.
- [14] N. Tug, M.A. Sargin, M. Yassa, Multidose methotrexate treatment of ectopic pregnancies with high initial  $\beta$ -human chorionic gonadotropin: can success be predicted? *Gynecol. Obstet. Investig.* 84 (1) (2019) 56–63.
- [15] E.A. Bachman, K. Barnhart, Medical management of ectopic pregnancy: a comparison of regimens, *Clin. Obstet. Gynecol.* 55 (2) (2012 Jun) 440–447.
- [16] V. Dadhwal, D. Deka, B. Ghosh, S. Mittal, Successful management of live ectopic pregnancy with high beta-hCG titres by ultrasound-guided potassium chloride injection and systemic methotrexate, *Arch. Gynecol. Obstet.* 280 (5) (2009 Nov) 799–801.
- [17] Z.S. Ozkan, B. Kumbak, E. Sapmaz, M. Simsek, Myometrial cystic formation after local methotrexate application into cornual gestational sac: a case report of an unexpected complication, *Case Rep. Obstet. Gynecol.* 61 (2011) 90–94.