



Successful hysteroscopic management of two cases of interstitial pregnancy

Uspešno histeroskopsko rešavanje dva slučaja intersticijalne trudnoće

Predrag Jokanović, Aleksandar Rakić

Clinic for Gynecology and Obstetrics “Narodni front”, Belgrade, Serbia

Abstract

Introduction. Interstitial pregnancy (IP) is the rarest type of tubal pregnancy with a high rupture rate and often remains asymptomatic in the first 10–12 gestational weeks. Therefore, the timing of the diagnosis is crucial for successful management. **Case report.** Two patients, aged 28 and 22, were diagnosed with IP using transvaginal ultrasound. Both patients were asymptomatic, with initial serum β hCG of 6,664 mIU/mL and 4,641 mIU/mL, respectively. Since they refused treatment with methotrexate and wanted to preserve their fertility, we performed operative hysteroscopy with resection and evacuation of the gestational tissue. The procedures were uneventful. The β hCG levels dropped significantly, and the patients were discharged after three and four hospital days, respectively. **Conclusion.** Using hysteroscopic procedures, we successfully treated two asymptomatic patients with IP of gestational age < 10 weeks by ultrasonography and levels of serum β hCG < 7,000 mIU/mL. With the occurrence of IP but also the numerous advantages of hysteroscopy, large, multicenter studies are necessary to further investigate the place of this approach as a single treatment method for IP. Trends and consequences observed during the COVID-19 pandemic correlate with the importance of timely diagnosis of ectopic pregnancies, the benefits of a minimally invasive approach in their treatment, and epidemiologically justified shorter hospital stays.

Key words:

gynecologic surgical procedures; minimally invasive surgical procedures; pregnancy, ectopic.

Apstrakt

Uvod. Intersticijalna trudnoća (IT) je najređa forma tubarne trudnoće koja ima visoku stopu rupture i često ostaje asimptomatska u prvih 10–12 nedelja gestacije. Stoga, vreme kada se postavi dijagnoza je ključno za uspešno lečenje. **Prikaz bolesnika.** Kod dve pacijentkinje, starosti 28 i 22 godine, ultrazvučno je dijagnostikovana IT. Obe pacijentkinje bile su bez simptoma, a koncentracije njihovog serumskog β hCG-a iznosile su 6 664 odnosno 4 641 mIU/mL. S obzirom na to da su odbile lečenje metotreksatom i imale želju da sačuvaju svoju fertilitet, podvrgnute su histeroskopskoj resekciji i evakuaciji gestacijskog tkiva. Operativne procedure su prošle bez komplikacija. Nakon operacija, značajno su snižene koncentracije β hCG-a u serumu i pacijentkinje su otpuštene trećeg, odnosno četvrtog postoperativnog dana. **Zaključak.** Primenom histeroskopske resekcije uspešno smo rešili IT kod dve pacijentkinje bez simptoma, sa IT gestacijske starosti kraće od 10 nedelja i nivoima serumskih β hCG-a nižim od 7 000 mIU/mL. S obzirom na izuzetno retku pojavu IT, ali i mnogobrojne prednosti histeroskopije, neophodne su obimne, multicentrične studije, da bi se ispitali mesto i značaj tog pristupa u rešavanju IT. Obrasci i posledice uočeni tokom COVID-19 pandemije su u korelaciji sa značajem pravovremene dijagnostike ektoičnih trudnoća, minimalno invazivnim pristupom u njihovom rešavanju i epidemiološki opravdanom kraćom hospitalizacijom.

Ključne reči:

hirurgija, ginekološka, procedure; hirurgija, minimalno invazivne procedure; trudnoća, ektoična.

Introduction

Despite the ongoing confusion regarding the terminology used by practitioners and scholars, interstitial, angular, and cornual pregnancies represent the specific types of pregnancies with contrasting prognoses and management routes.

According to the literature, interstitial pregnancy (IP) is the rarest type of tubal pregnancy and accounts for about 2–4% of

all ectopic pregnancies (EPs) ¹. Regardless of its incidence, IPs account for about 20% of deaths related to EPs ^{1,2}. The presence of the gestational sac in the proximal part of the fallopian tube surrounded by a thin layer of muscular fibers of the uterus reportedly has a rupture rate of almost 14% ^{1,2}. These reported percentages, and the fact that most IPs remain asymptomatic until 7 to 12 weeks of gestation, urge for the correct and prompt diagnosis and an adequate method of clinical management.

Many factors determine the adequate treatment of IP. Of these, the most important is the presence of life-threatening signs and symptoms. Therefore, the timing of the diagnosis is crucial. The patient's age and fertility should always be considered in choosing the best treatment option. Nowadays, the combination of serial measurements of serum human beta chorionic gonadotropin (β hCG) and three-dimensional transvaginal ultrasound significantly shorten the time needed for the correct diagnosis and provide a more conservative approach, either medical or surgical³. In the era of modern gynecology, endoscopy is considered a golden standard for the treatment of EPs in unusual locations⁴. Literature reports laparoscopy, hysteroscopy, and methotrexate (MTX) as single or combined options in treating IPs.

We present two cases of IPs successfully managed solely by operative hysteroscopy.

Case report

Case I

A 28-year-old patient, para 4, gravida 5, was admitted to the Clinic under the ultrasonographic suspicion of EP. The period of amenorrhoea was eight weeks. The initial value of serum β hCG was 6,664 mIU/mL [reference range (RR) < 5.00 mIU/mL; for gestational weeks 1–10, RR is 202.00 – 231,000.00 mIU/mL]. An ultrasonographic exam revealed a gestational sac of 20 mm in diameter in the right uterine *cornua* with the interstitial sign (Figure 1A). There were no signs

of intrauterine pregnancy, and both adnexa appeared morphologically normal. The pouch of Douglas and the vesicouterine space were free of any fluid. The patient showed no symptoms of pain, bleeding, or weakness. A laboratory exam did not show any signs of blood loss. Considering the patient's age and future fertility, along with the ultrasonographic and clinical features, we performed diagnostic hysteroscopy. Under general anesthesia, a 10 mm operative hysteroscopy revealed an empty uterine cavity, with the decidual transformation of the endometrium and a gestational sac in the region of the right uterine *cornua* (Figure 1B). The gestational sac was resected and then evacuated from the uterine cavity using a 5Fr hysteroscopic resectoscope. A bipolar electrode was used for the hemostasis. The blood loss was insignificant. Levels of β hCG significantly dropped two days after the procedure (611 mIU/mL), and the patient was discharged.

Case II

A 22-year-old patient, para 0, gravida 0, was referred from the primary healthcare unit with the diagnosis of a missed abortion. The period of amenorrhoea was eleven weeks. Serum β hCG was 4,641 mIU/mL (for gestational weeks 11–15, RR is 22,536.00–234,990.00 mIU/mL). The patient did not complain of any symptoms. At the ultrasonographic exam, there were no signs of intrauterine pregnancy. A gestational sac of 47 mm, with an embryo whose crown-rump length was 3.5 mm, without cardiac activity, was seen in the right uterine *cornua* (Figure 2A). Bearing in

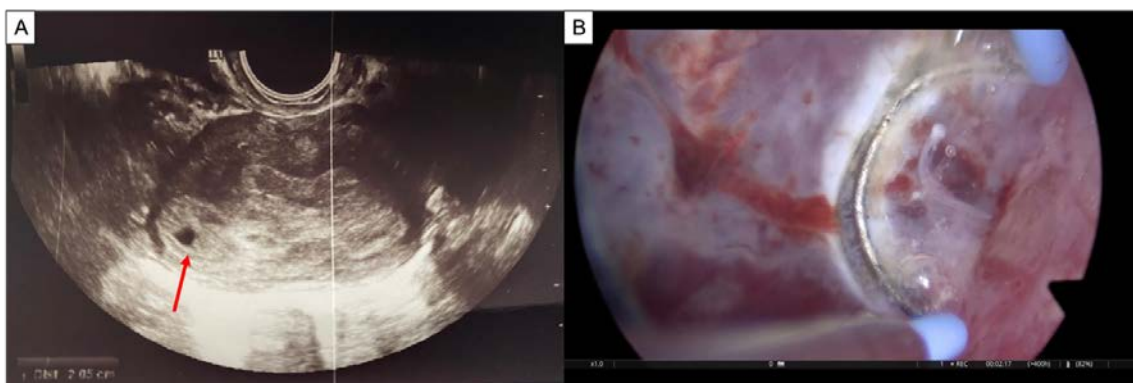


Fig. 1 – A) Ultrasonographic feature from Case I: a gestational sac of 20 mm (red arrow) in the right uterine *cornua* with the interstitial sign; B) View of the gestational sac at the moment of hysteroscopic resection.

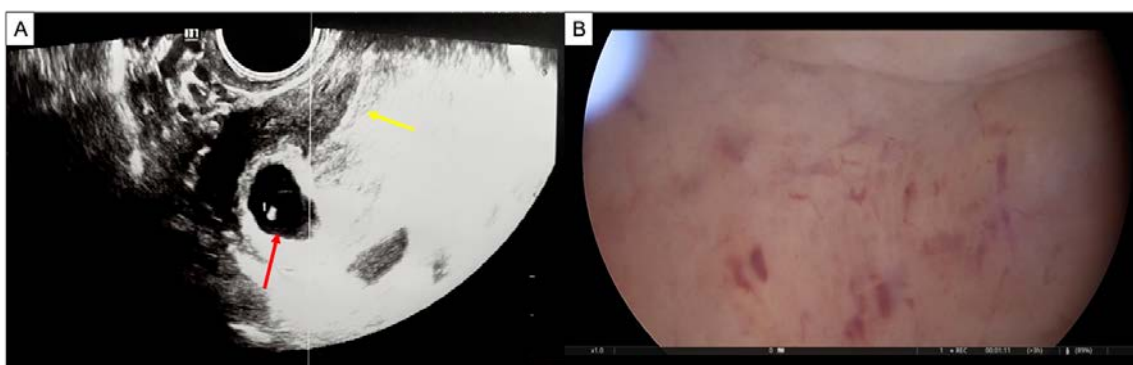


Fig. 2 – A) Ultrasonographic feature from Case II: gestational sac of 47 mm (red arrow), with an embryo, crown-rump length of 3.5 mm, without cardiac activity, in the right uterine *cornua* alongside an empty uterine cavity (yellow arrow); B) Hysteroscopic view of an empty uterine cavity.

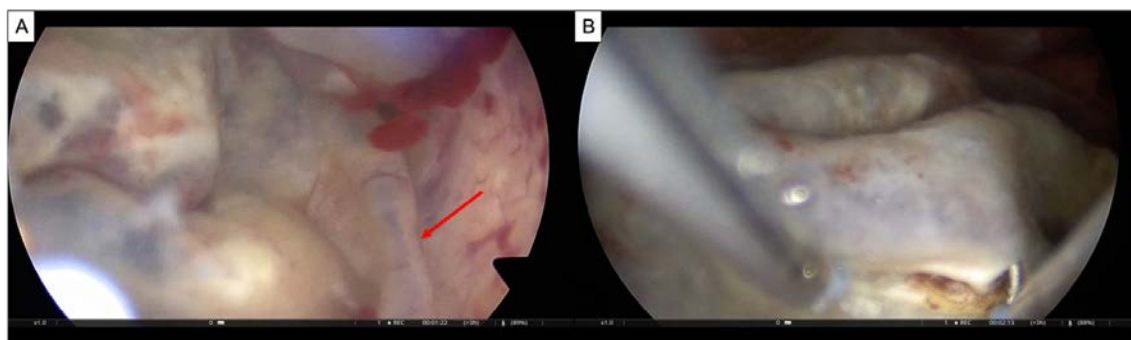


Fig. 3 – A) Hysteroscopic view of distended right uterine *cornua* with the collapsed gestational tissue in the second patient; B) Hysteroscopic resection of the gestational tissue.

Table 1

Patients' obstetric history, onset features, duration of the procedures, and hemoglobin (Hgb) levels

Pts	Age (years)	Obstetric history	Serum β hCG (mIU/mL)	Onset symptoms	Ultrasonographic feature(s)	Duration of the procedure (min)	¹ Hgb before the procedure (g/L)	Hgb after the procedure (g/L)	Hospital days
I	28	P4G5	6,664	none	A gestational sac of 20 mm in diameter in the right uterine <i>cornua</i> , with the interstitial sign.	13	150	124	4
II	22	P0G0	4,641	none	A gestational sac of 47 mm in the right uterine <i>cornua</i> , with an embryo whose CRL was 3.5 mm, without cardiac activity.	27	141	122	3

¹ Note: reference range for hemoglobin (Hgb) is 119–157 g/L.

Pts – patients; β hCG – beta chorionic gonadotropin; CRL – crown-lump length.

mind the patient's obstetrical history and future fertility, a diagnostic hysteroscopy was arranged. Hysteroscopy revealed an empty uterine cavity (Figure 2B) and distended right uterine *cornua* with collapsed gestational tissue (Figure 3A). Using the same approach described in the previous patient, gestational tissue was resected (Figure 3B) and evacuated from the uterine *cornua*. The blood loss during the procedure was negligible. Serum β hCG level saw a significant drop following the procedure, and the patient was discharged on the second postoperative day.

Obstetrical history, ultrasonographic findings, initial serum β hCG concentrations, number of hospital days, and levels of hemoglobin (Hgb) before and after the procedure for both patients are presented in Table 1.

Discussion

As previously mentioned, distinguishing the IP and eccentric intrauterine pregnancies (cornual and angular pregnancies) is essential. Angular pregnancy, the implantation of the gestational sac in the lateral angle of the uterine cavity, medially to the uterotubal junction, is a form of the eccentric intrauterine pregnancy with a live birth rate of 25–80%^{1,5}.

Cornual pregnancy represents the presence of the gestational sac in the rudimentary horn of the uterus with the Mullerian anomaly. There are several proposed ultrasonographic criteria for the correct diagnosis of IP: empty uterine cavity, gestational sac separated from the lateral edge of the cavity and surrounded by a thin myometrial layer (introduced in the 1990s by Timor-Tritsch et al.⁶), and interstitial line sign⁷. Combined with the double sac sign, these criteria can distinguish IP and eccentric pregnancies with a specificity of 100%¹. The importance of distinguishing between these entities lies in the fact that IP has a two-fold higher mortality rate compared to other EPs³.

There are few reported methods for the successful treatment of IP. The most conservative, expectant method, is not recommended because of the known, life-threatening complications of the IP.

Medical treatment with systemic or local injection of MTX is widely described as an optimal method for patients who wish to preserve their fertility. Nevertheless, this treatment option has a failure rate of 9–65%⁸. Moreover, systemic administration of MTX could cause serious side effects. Additionally, this conservative medical option should be used with caution in cases when β hCG > 5,000 mIU/mL and

the identified gestational sac is $> 5\text{cm}$ ⁸. Ultrasonography-guided local instillation of the potassium chloride was recently described as a novel alternative after unsuccessful MTX treatment of IP ⁹.

Since the operator can see and treat the pathology found during the procedure, hysteroscopy is considered a golden standard in managing intrauterine pathology. Compared to MTX, hysteroscopy requires less time for the normalization of βhCG levels and shorter hospital stays in EP treatment ¹⁰. One of the first described cases of hysteroscopic management of IP was published by Meyer and Mithcell ¹¹. Following this report, hysteroscopy was often performed combined with laparoscopy for managing IP. In a systematic literature review, D'hoore et al. reported 8 articles describing the hysteroscopic treatment of IP or interstitially located retained products of conception, including their case report ¹². None of the published cases or case series used hysteroscopic resection and evacuation of the gestational tissue as a single treatment option. We have identified nine additional published papers regarding the management of IP. Besides four papers regarding the laparoscopic approach, one laparotomy, and one MTX treatment, one group of authors reported successfully combined laparoscopic and hysteroscopic treatment of IP. In a case series of laparoscopic-assisted hysteroscopic removal of IP, Niu et al. ¹³ concluded that if the mass distends the uterine *cornua* with a tunnel connecting the mass and the *cornua*, hysteroscopic resection is likely to be successful. In a series of five patients, Casadio et al. ¹⁴ successfully treated IP with local hysteroscopic MTX injection. Hysteroscopic-assisted local MTX injection could minimize adverse systemic effects of MTX ^{14, 15}. This modality, combined with our report of two cases, seems promising for managing IP. Hysteroscopy, with or without local MTX injection, should be a subject for future studies to determine whether it could be used without the need for laparoscopic assistance.

Furthermore, detailed investigations are necessary to identify the patients most suitable for this modality. With the precise identification of suitable patients, the main advantages of hysteroscopic treatment alone could be seen in the short duration of the procedure, fewer hospital days, and the ability for the patients to conceive shortly after the next menstrual cycle.

The main limitation of our study is the small number of subjects. Even though we successfully treated two patients with IP using operative hysteroscopy, future multicenter-based studies with a significantly larger number of women with IP treated solely with this procedure are needed. More-

over, along with more subjects, the potential benefits of hysteroscopy compared to medical or invasive surgical treatment of IP could be observed in well-designed comparative studies. On the other hand, the occurrence of IP presents the main obstacle to overcoming the mentioned limitations.

Additionally, we have observed another potential advantage of the endoscopic treatment of EPs, along with the IPs. Several authors have pointed out the higher rates of the ruptures of EPs during the COVID-19 pandemic compared to the period before the pandemic ¹⁶⁻¹⁸. Authors reported delayed presentation of EPs along with an increase in blood loss in patients treated surgically ^{19, 20}. The exact cause of this trend is yet to be confirmed, but the disruption of primary healthcare, women's fear of exposure, and reduced medical checkups together could be the underlying explanation ¹⁹. Lastly, a study from Brazil noted that SARS-CoV-2-positive patients with EP should be treated surgically since MTX could reduce immunity, and the pulmonary disease itself represents a contraindication for this treatment ²¹. In the study regarding the hysteroscopic treatment of cervical pregnancies, the authors noted shorter hospital stays, reduced blood loss, and shorter time needed for recovery ²². Even though our study has the crucial limitation of only two cases, the advantages of the hysteroscopic approach should be emphasized even more during the COVID-19 pandemic.

Conclusion

We have successfully treated two asymptomatic, clinically stable patients with IP of gestational age less than 10 weeks by ultrasonography and serum $\beta\text{hCG} < 7,000$ mIU/mL. With numerous advantages of the minimally invasive approaches to EP treatment, large, multicenter, and comparative studies should be performed to further investigate the place of hysteroscopy as a single treatment method for IP. Moreover, during the ongoing pandemic, where we experience the disruption of the health system and observe the trend of EPs that require emergency surgical treatment, the place and advantages of the minimally invasive approach should be highlighted. Consequences and trends observed during the COVID-19 pandemic correlate with the importance of timely diagnosis of EPs, the benefits of a minimally invasive approach in their treatment, and epidemiologically justified shorter hospital stays.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. *Finlinson AR, Bollig KJ, Schust DJ*. Differentiating pregnancies near the uterotubal junction (angular, cornual, and interstitial): a review and recommendations. *Fertil Res Pract* 2020; 6: 8.
2. *Tang A, Baartz D, Khoo SK*. A medical management of interstitial ectopic pregnancy: A 5-year clinical study. *Aust N Z J Obstet Gynaecol* 2006; 46(2): 107-11.
3. *Lin TY, Chueh HY, Chang SD, Yang CY*. Interstitial ectopic pregnancy: A more confident diagnosis with three-dimensional sonography. *Taiwan J Obstet Gynecol* 2021; 60(1): 173-6.
4. *Wang YL, Weng SS, Huang WC, Su TH*. Laparoscopic management of ectopic pregnancies in unusual locations. *Taiwan J Obstet Gynecol* 2014; 53(4): 466-70.

5. Jansen RP, Elliott PM. Angular intrauterine pregnancy. *Obstet Gynecol* 1981; 58(2): 167–75.
6. Timor-Tritsch IE, Monteagudo A, Matera C, Veit CR. Sonographic evolution of cornual pregnancies treated without surgery. *Obstet Gynecol* 1992; 79(6): 1044–9.
7. Ackerman TE, Levi CS, Dashefsky SM, Holt SC, Lindsay DJ. Interstitial line: sonographic finding in interstitial (cornual) ectopic pregnancy. *Radiology* 1993; 189(1): 83–7.
8. Dagar M, Srivastava M, Ganguli I, Bhardwaj P, Sharma N, Chawla D. Interstitial and Cornual Ectopic Pregnancy: Conservative Surgical and Medical Management. *J Obstet Gynaecol India* 2018; 68(6): 471–6.
9. Shetty V, Shivananda RP, Vasudeva A, Shetty J. Successful management of three cases of interstitial pregnancies with local instillation of potassium chloride: avoiding a potential cornuostomy. *BMJ Case Rep* 2021; 14(3): e239918.
10. Stabile G, Mangino FP, Romano F, Zinicola G, Ricci G. Ectopic Cervical Pregnancy: Treatment Route. *Medicina (Kaunas)* 2020; 56(6): 293.
11. Meyer WR, Mitchell DE. Hysteroscopic removal of an interstitial ectopic gestation. A case report. *J Reprod Med* 1989; 34(11): 928–9.
12. D'hoore E, D'hoore L, Van den Berghe S, Roets E, van Wessel S, Hamerlynck T. Operative hysteroscopy in the minimally invasive management of interstitial pregnancy and interstitially retained products of conception: A case report and systematic literature review. *Eur J Obstet Gynecol Reprod Biol* 2021; 265: 54–9.
13. Niu X, Tang Y, Li S, Ni S, Zheng W, Huang L. The feasibility of laparoscopically assisted, hysteroscopic removal of interstitial pregnancies: A case series. *J Obstet Gynaecol Res* 2021; 47(10): 3447–55.
14. Casadio P, Arena A, Verrelli L, Ambrosio M, Fabbri M, Giovannico K, et al. Methotrexate injection for interstitial pregnancy: Hysteroscopic conservative mini-invasive approach. *Facts Views Vis Obgyn* 2021; 13(1): 73–6.
15. Leggieri C, Guasina F, Casadio P, Arena A, Pilu G, Seracchioli R. Hysteroscopic Methotrexate Injection Under Ultrasonographic Guidance for Interstitial Pregnancy. *J Minim Invasive Gynecol* 2016; 23(7): 1195–9.
16. Casadio P, Youssef A, Arena A, Gamal N, Pilu G, Seracchioli R. Increased rate of ruptured ectopic pregnancy in COVID-19 pandemic: analysis from the North of Italy. *Ultrasound Obstet Gynecol* 2020; 56(2): 289.
17. Werner S, Katz A. Change in ectopic pregnancy presentations during the covid-19 pandemic. *Int J Clin Pract* 2021; 75(5): e13925.
18. Chmielewska B, Barratt I, Townsend R, Kalafat E, van der Meulen J, Guroł-Urganci I, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health* 2021; 9(6): e759–e772.
19. Dvash S, Cuckle H, Smorgick N, Vaknin Z, Padoa A, Maymon R. Increase rate of ruptured tubal ectopic pregnancy during the COVID-19 pandemic. *Eur J Obstet Gynecol Reprod Biol* 2021; 259: 95–9.
20. Barg M, Rotem R, Mor P, Rottenstreich M, Khatib F, Grisaru-Granovsky S, et al. Delayed presentation of ectopic pregnancy during the COVID-19 pandemic: A retrospective study of a collateral effect. *Int J Gynaecol Obstet* 2021; 153(3): 457–61.
21. Elito Júnior J, Araujo Júnior E. Medical Treatment for Ectopic Pregnancy during the COVID-19 Pandemic. *Rev Bras Ginecol Obstet* 2020; 42(12): 849–50.
22. Maglic R, Rakic A, Nikolic B, Maglic D, Jokanovic P, Mibajlovic S. Management of Cervical Ectopic Pregnancy with Small-Caliber Hysteroscopy. *JSLs* 2021; 25(2): e2021.00016.

Received on December 27, 2021

Revised on February 1, 2022

Accepted on February 16, 2022

Online First February 2022