EDORIUM Journals

J Case Rep Images Obstet Gynecol 2025;11(1):53–57.
www.ijcriog.com

CASE REPORT PEER REVIEWED | OPEN ACCESS

Twin tubal and interstitial ectopic pregnancies managed by multidose methotrexate therapy

Jessica Shu Nan Li, Romina Levy, Jeffrey Man Hay Wong

ABSTRACT

Introduction: Twin ectopic pregnancy is a rare diagnosis with no clear consensus guidelines for management. We present a case of a stable patient with a spontaneous twin interstitial and tubal ectopic pregnancy treated with systemic multidose methotrexate.

Case Report: A 31-year-old nulliparous patient was diagnosed with a twin interstitial and tubal ectopic pregnancy after presenting at 6+1 weeks gestational age with a β-hCG of 2303 mIU/mL, vaginal spotting, and mild pain. Given the case characteristics and hemodynamic stability, she was managed with systemic multidose methotrexate and leucovorin rescue. She remained clinically stable and her β-hCG became undetectable on day 42 after treatment initiation.

Conclusion: Multidose methotrexate therapy is a suitable treatment option for carefully selected patients with twin ectopic pregnancies who are hemodynamically stable.

Keywords: Ectopic pregnancy, Interstitial pregnancy, Methotrexate, Tubal pregnancy, Twin ectopic pregnancy

How to cite this article

Li JSN, Levy R, Wong JMH. Twin tubal and interstitial ectopic pregnancies managed by multidose methotrexate therapy. J Case Rep Images Obstet Gynecol 2025;11(1):53–57.

Jessica Shu Nan Li[1], MD, MPH, Romina Levy[2], MD, Jeffrey Man Hay Wong[2], MD

Affiliations: [1]Department of Obstetrics and Gynaecology, University of Toronto, Toronto, Ontario, Canada; [2]Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver, British Columbia, Canada.

Corresponding Author: Dr. Jessica Shu Nan Li, Department of Obstetrics and Gynaecology, University of Toronto Suite 1200, 123 Edward Street, Toronto, Ontario M5G 1E2, Canada; E-mail: jli512@student.ubc.ca

Received: 03 February 2025
Accepted: 11 March 2025
Published: 02 April 2025

Article ID: 100199Z08JL2025

****

doi: 10.5348/100199Z08JL2025CR

INTRODUCTION

Ectopic pregnancy, defined as a gestation where the blastocyst implants outside of the uterine cavity, accounts for 1–2% of all pregnancies [1, 2]. Unilateral twin tubal ectopic pregnancy occurs between 1 in 20,000 and 1 in 125,000 for live gestations [3, 4]. The incidence of multi-gestation ectopic pregnancy with other implantation sites is unknown, given its rarity. Risk factors for ectopic implantation include current intrauterine device, underlying tubal pathology, infection, inflammation, endometriosis, and previous ectopic pregnancy [2, 5, 6].

Among all ectopic pregnancies, 2–3% implant in the interstitial region of the fallopian tube [2, 6]. Interstitial ectopic pregnancies (IEPs) are associated with greater morbidity and mortality, due to the adjacent vascular anastomosis of the uterine and ovarian arteries and greater myometrial distensibility leading to delayed presentations [7, 8]. For these reasons, IEPs have a 2.5% mortality rate, seven times that of ectopic pregnancies overall [7, 9, 10].

Management approach for ectopic pregnancy depends on several factors, including patient characteristics and stability, initial β-human chorionic gonadotropin (β-hCG) levels, and ultrasound findings. There is no consensus for multi-gestation ectopic pregnancies. Given the lack of clear guidelines and the rarity of these implantations, we report a case of a twin ectopic pregnancy with simultaneous interstitial and tubal implantations in a hemodynamically stable patient, who was successfully treated with systemic multidose methotrexate regimen. We also describe a range of management strategies reported in the literature for twin ectopic pregnancies.

CASE REPORT

A 31-year-old, gravida 2, para 0, abortus 1 female presented to an early pregnancy assessment clinic (EPAC) at 6+1 weeks gestational age by last menstrual period

with a one-week history of vaginal spotting and mild lower pelvic pain. This pregnancy was a spontaneous conception. Her obstetrical history was significant for an expectantly managed first-trimester spontaneous abortion. She was otherwise healthy with no previous surgeries. Two days prior to her presentation, hemoglobin and β-hCG in the community were 13.6 g/dL and 1436 mIU/mL, respectively. At EPAC, her hemoglobin and β-hCG were 13.8 g/dL and 2303 mIU/mL, respectively. An ultrasound demonstrated a left echogenic adnexal mass with peripheral vascularity measuring 16×13 mm with a thickened, heterogeneous endometrium measuring 13 mm, and a moderate amount of free fluid in the cul-de-sac suggestive of hemoperitoneum. Due to the high suspicion for an ectopic pregnancy, she was transferred to our tertiary care hospital.

At our hospital, she continued to have minimal vaginal spotting, but her pain resolved. Her vital signs were stable. Her abdomen was soft and non-tender. A repeat ultrasound similarly demonstrated a 20 mm thickened endometrium with no gestational sac, and a 17×15 mm left adnexal mass with echogenic rind and peripheral vascularity (Figure 1). However, an additional 8×7×5 mm cystic lesion with an echogenic rind and peripheral vascularity was noted at the left cornua with the overlying myometrium measuring 3 mm (Figure 2). No interstitial line sign and no fetal heart rate were noted. There was a small amount of free fluid in the cul-de-sac and left adnexa with low-level internal echoes.

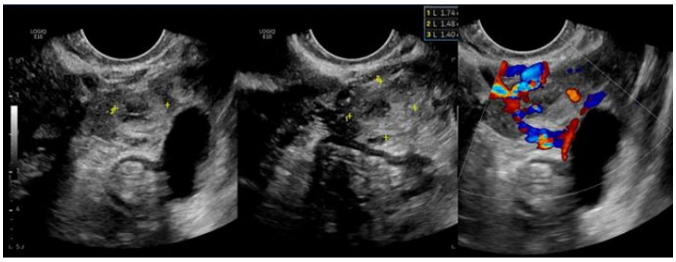


Figure 1: Left adnexal lesion measuring 17×15 mm with echogenic rind and peripheral vascularity, suggestive of left tubal ectopic pregnancy.

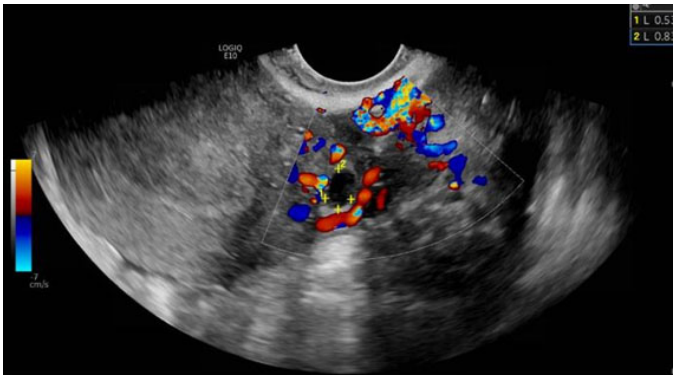


Figure 2: Cystic lesion with peripheral vascularity and echogenic rind measuring 8×5 mm with the overlying myometrium measuring 3 mm, suggestive of a concurrent left interstitial ectopic pregnancy.

Upon review with radiology, the consensus diagnosis was a twin ectopic pregnancy with implantations in both the left interstitial region and the left fallopian tube. There was no concurrent viable intrauterine pregnancy. The patient was admitted for multidose methotrexate (intramuscular 1 mg/kg) on days 1, 3, 5, and 7, and leucovorin (intramuscular 0.1 mg/kg) on days 2, 4, 6, 8. This is our institution's standard protocol for managing interstitial pregnancies, and is consistent with current society recommendations. During admission, she remained hemodynamically stable with minimal vaginal bleeding and abdominal pain. Her β-hCG peaked at 3213 mIU/mL on day 5 but subsequently dropped to 2187 mIU/mL by day 9 (Table 1).

Table 1: Patient's β-human chorionic gonadotropin (β-hCG) and hemoglobin during investigation and treatment

	β-hCG (mIU/mL)	Hemoglobin (g/dL)
Two days prior to presentation/treatment	1436	13.6
Day 1 (EPAC)	2303	13.8
Day 1 (Hospital) (MTX #1)	2204	12.7
Day 3 (MTX #2)	2860	13.0
Day 5 (MTX #3)	3213	11.5
Day 6	2750	11.4
Day 7 (MTX #4)	2817	11.7
Day 9	2178	11.4
Day 13	1446*	N/A
Day 17	949**	11.5
Day 19	1316*	N/A
Day 20	882	12.2
Day 28	185	N/A
Day 35	12	N/A
Day 42	<1	N/A

*β-hCG levels measured at outpatient lab rather than hospital lab.

**The patient developed mild abdominal pain and light vaginal bleeding.

Abbreviations: EPAC: early pregnancy assessment clinic; MTX: methotrexate; N/A: not applicable.

A repeat ultrasound on day 7 continued to show a left tubal ectopic pregnancy measuring 26×20×16 mm and a left cornual pregnancy measuring 9×7×6 mm with no free fluid. Given the drop in β-hCG and clinical stability, she was discharged on day 9 with weekly outpatient β-hCG surveillance.

The patient required two additional outpatient investigations outside of our standard protocol. On treatment day 17, she developed mild abdominal pain and light vaginal bleeding, prompting an ultrasound which demonstrated the left tubal pregnancy measuring 3734×30 mm and the interstitial ectopic measuring 9×9×7 mm with a small amount of simple fluid. Her β-hCG level was 949 mIU/mL. Given her stability and decreasing

β-hCG, she was expectantly managed. On treatment day 19, her β-hCG level increased to 1316 mIU/mL. However, the β-hCG decreased to 882 mIU/mL when repeated on the same day, and she remained asymptomatic. On day 42, her β-hCG levels were undetectable and she was discharged from care.

Following this twin ectopic pregnancy, the patient subsequently had one spontaneous abortion and a vacuum-assisted vaginal delivery two years later.

DISCUSSION

Our case demonstrates the successful treatment of a stable patient with a twin interstitial and tubal ectopic pregnancy using systemic multidose methotrexate. As twin ectopic pregnancy is a rare diagnosis, there is no consensus for management. We applied the multidose protocol for singleton IEP, given that one of the gestations was interstitial. This decision was made with consideration of this patient's hemodynamic stability, lack of signs for rupture, low initial β-hCG, desire to avoid surgical management, and sonographic features of twin ectopic gestations.

To our knowledge, there are no published cases of twin ectopic pregnancies with unilateral tubal and interstitial implantations, in the absence of an intrauterine gestation. We reviewed the literature for twin ectopic pregnancies with other patterns of implantation, including twin tubal ectopic pregnancies and twin IEPs. Management strategies for these included medical management with methotrexate, combined medical and surgical treatment, or surgical alone.

The most similar case includes a tubal and interstitial ectopic pregnancy—but with a concurrent intrauterine twin pregnancy. Given the wanted intrauterine pregnancies, systemic medical management with methotrexate was unacceptable, so the interstitial gestation was treated by ultrasound-guided KCl injection, and the tubal pregnancy was managed with laparoscopic salpingectomy [11].

While twin tubal ectopic pregnancies have been successfully medically managed, significant variation exists in both dosing and scheduling of methotrexate. Fernandez et al. reported a case of a unilateral twin tubal ectopic pregnancy treated with methotrexate, with an initial β-hCG of 3640 mIU/mL [12]. Their regimen consisted of an ultrasound-guided methotrexate injection into each gestational sac, and a dose of intramuscular methotrexate 48 hours later. Meanwhile, Karadeniz et al. reported a case of a unilateral twin tubal ectopic with an initial β-hCG of 987 mIU/mL that was successfully treated with systemic multidose methotrexate, with an additional dose of methotrexate (1 mg/kg) on day 14, as β-hCG reached 1200 IU/mL [13]. Another case of a 7-week twin tubal ectopic pregnancy with an initial β-hCG of 18,780 mIU/mL was successfully treated with a single-dose of 1 mg/kg methotrexate intramuscularly [14].

Successful medical treatment of a twin IEP was first described by Karsdorp et al. (1992) in a case with a pre-treatment β-hCG level of 4400 mIU/mL, using three doses of systemic methotrexate and leucovorin to a cumulative amount of 900 mg of methotrexate [15].

Methotrexate has also shown to be effective for treating twin IEPs when given both locally into the gestational sacs and systemically as a single dose [16].

Several cases have also been reported where medical management failed and subsequent surgical intervention was required. A twin tubal ectopic with an initial β-hCG of 13,217 mIU/mL was initially treated with systemic methotrexate (50 mg/m^2) and folinic acid rescue (three doses given on days 1, 7, and 14), but subsequently required emergent laparoscopic salpingectomy due to tubal rupture [17]. In a twin IEP with an initial β-hCG of 15,022 mIU/mL, one embryo remained viable after four courses of methotrexate/leucovorin, requiring an additional 50 mg of methotrexate intramurally during laparoscopy and four additional doses intramuscularly postoperatively [18]. Other therapeutic approaches for twin IEPs included uterine artery embolization after failing systemic multidose methotrexate (initial β-hCG levels 33,689 and 49,997 mIU/mL, respectively) [19, 20], and salpingectomy and resection of the interstitial section after failing multidose methotrexate (initial β-hCG level 60,348 mIU/mL) [21]. A commonality of these failed medical treatments is higher pretreatment β-hCG level.

Finally, surgical-only treatment of twin IEP with cornual wedge resection, laparoscopic automatic stapler, and conical exeresis of the cornual section have been reported [22–24]. Surgical management was more common when there was fetal cardiac activity. In 2021, Martin et al. reported a case of a live twin tubal ectopic pregnancy treated by laparoscopic salpingectomy due to fetal cardiac activity [25]. They further identified 21 cases in the literature of live twin ectopic pregnancies, all managed surgically or with a combination of medical and surgical treatment.

Given the study design, this case report has limited generalizability to the general population. The findings and regimen here may not be applicable to other types of twin ectopic implantation locations and patient populations, and careful patient selection is warranted.

CONCLUSION

In conclusion, we demonstrate successful application of the systemic multidose methotrexate treatment protocol to a unique implantation of twin ectopic pregnancy. We conclude that the multidose methotrexate regimen is a suitable option for patients presenting with similar twin ectopic pregnancies and may be considered when one gestation is interstitial. We suggest consideration of this protocol for patients with twin ectopic pregnancies without a concurrent viable intrauterine pregnancy, who are hemodynamically stable, have a low pre-treatment β-hCG without contraindications to methotrexate, and who are compliant with follow-up. The applicability of this protocol to twin ectopic pregnancies with other

implantation sites, higher initial β-hCG levels, or presence of cardiac activity requires further research.

REFERENCES

1. Po L, Thomas J, Mills K, et al. Guideline No. 414: Management of pregnancy of unknown location and tubal and nontubal ectopic pregnancy. J Obstet Gynaecol Can 2021;43(5):614–30.e1.
2. Moawad NS, Mahajan ST, Moniz MH, Taylor SE, Hurd WW. Current diagnosis and treatment of interstitial pregnancy. Am J Obstet Gynecol 2010;202(1):15–29.
3. Rolle CJ, Wai CY, Bawdon R, Santos-Ramos R, Hoffman B. Unilateral twin ectopic pregnancy in a patient with a history of multiple sexually transmitted infections. Infect Dis Obstet Gynecol 2006;2006:10306.
4. Parker J, Hewson AD, Calder-Mason T, Lai J. Transvaginal ultrasound diagnosis of a live twin tubal ectopic pregnancy. Australas Radiol 1999;43(1):95–7.
5. Marion LL, Meeks GR. Ectopic pregnancy: History, incidence, epidemiology, and risk factors. Clin Obstet Gynecol 2012;55(2):376–86.
6. Bouyer J, Coste J, Fernandez H, Pouly JL, Job-Spira N. Sites of ectopic pregnancy: A 10 year population-based study of 1800 cases. Hum Reprod 2002;17(12):3224–30.
7. Faraj R, Steel M. Management of cornual (interstitial) pregnancy. The Obstetrician & Gynaecologist 2007;9(4):249–55.
8. Rastogi R, Gl M, Rastogi N, Rastogi V. Interstitial ectopic pregnancy: A rare and difficult clinicosonographic diagnosis. J Hum Reprod Sci 2008;1(2):81–2.
9. Lau S, Tulandi T. Conservative medical and surgical management of interstitial ectopic pregnancy. Fertil Steril 1999;72(2):207–15.
10. Kirk E, Bottomley C, Bourne T. Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location. Hum Reprod Update 2014;20(2):250–61.
11. Kwon B, Kang S, Lee HJ, et al. Non-surgical management and obstetric outcomes of heterotopic interstitial pregnancies. Minim Invasive Ther Allied Technol 2020;29(6):375–9.
12. Fernandez H, Bourget P, Lelaidier C, Doumerc S, Frydman R. Methotrexate treatment of unilateral twin ectopic pregnancy: Case report and pharmacokinetic considerations. Ultrasound Obstet Gynecol 1993;3(5):357–9.
13. Karadeniz RS, Dilbaz S, Ozkan SD. Unilateral twin tubal pregnancy successfully treated with methotrexate. Int J Gynaecol Obstet 2008;102(2):171.
14. Arikan DC, Kiran G, Coskun A, Kostu B. Unilateral tubal twin ectopic pregnancy treated with single-dose methotrexate. Arch Gynecol Obstet 2011;283(2):397–9.
15. Karsdorp VH, Van der Veen F, Schats R, Boer-Meisel ME, Kenemans P. Successful treatment with methotrexate of five vital interstitial pregnancies. Hum Reprod 1992;7(8):1164–9.
16. Ragsdale ES, Rosner M, Gebb J, Bircaj E, Dar P. P26.12: Twin interstitial ectopic pregnancy: A case report. Ultrasound Obstet Gynecol 2014;44(Suppl 1):181–369.
17. Betti M, Vergani P, Damiani GR, et al. Unilateral twin tubal pregnancy: A case report and review of the literature. Acta Biomed 2018;89(3):423–7.
18. Klemm P, Koehler C, Eichhorn KH, Hillemanns P, Schneider A. Sonographic monitoring of systemic and local methotrexate (MTX) therapy in patients with intact interstitial pregnancies. J Perinat Med 2006;34(2):149–57.
19. Ophir E, Singer-Jordan J, Oettinger M, et al. Uterine artery embolization for management of interstitial twin ectopic pregnancy: Case report. Hum Reprod 2004;19(8):1774–7.
20. Berretta R, Merisio C, Dall'Asta A, et al. Conservative treatment for interstitial monochorionic twin pregnancy: Case report and review of the published work. J Obstet Gynaecol Res 2014;40(3):829–32.
21. Berkes E, Szendei G, Csabay L, Sipos Z, Joo JG, Rigo J Jr. Unilateral triplet ectopic pregnancy after in vitro fertilization and embryo transfer. Fertil Steril 2008;90(5):2003.e17–20.
22. Garretto D, Lee LN, Budorick NE, Figueroa R. Interstitial twin pregnancy: A unique case presentation. J Clin Ultrasound 2015;43(7):447–50.
23. Casadio P, Formelli G, Spagnolo E, et al. Laparoscopic treatment of interstitial twin pregnancy. Fertil Steril 2009;92(1):390.e13–7.
24. Ahsan Akhtar M, Izzat F, Keay SD. Laparoscopic management of interstitial pregnancy with automatic stapler. BMJ Case Rep 2012;2012:bcr2012006851.
25. Martin A, Balachandar K, Bland P. Management of a spontaneously conceived live unilateral twin ectopic pregnancy in Australia: A case report. Case Rep Womens Health 2021;30:e00300.

****

Author Contributions

Jessica Shu Nan Li – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Romina Levy – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jeffrey Man Hay Wong – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved

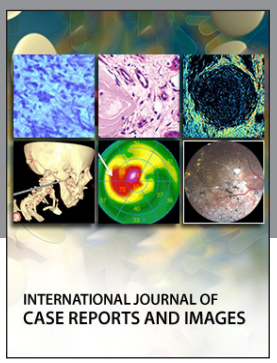
Guarantor of Submission
The corresponding author is the guarantor of submission.

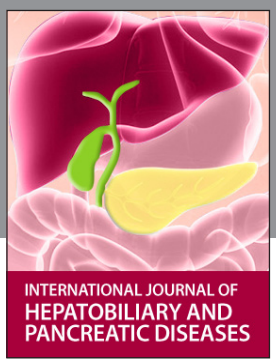
Source of Support
None.

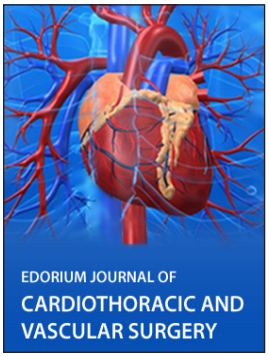
Consent Statement
Written informed consent was obtained from the patient for publication of this article.

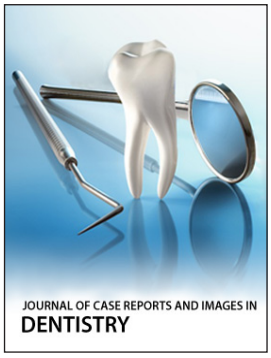
Conflict of Interest
Authors declare no conflict of interest.

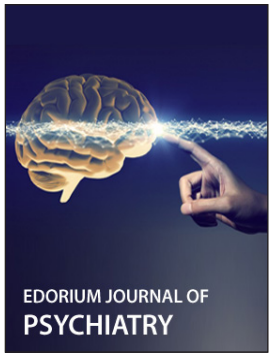
Data Availability
All relevant data are within the paper and its Supporting Information files.

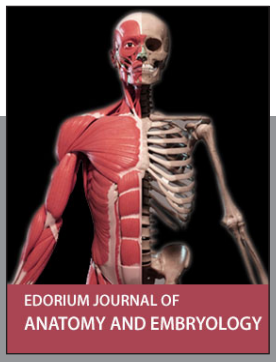


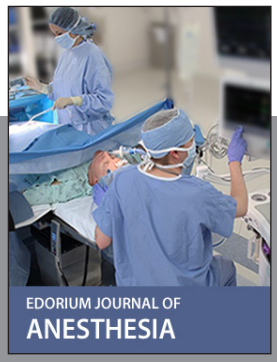












Submit your manuscripts at

www.edoriumjournals.com