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CASE REPORT

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Heterotopic pregnancy after a spontaneous conception a case report with a review of clinical, laboratory and imaging findings

Ahmed H. Abdelmonem[1,2] | **Gamal Sayed**[2,3,4,5] | **Abd Elwahid Abugazia**[6] | **Samah Kohla**[2,7] | **Reda Youssef**[2,8]

[1]Department of Radiology, Hamad General Hospital, Doha, Qatar

[2]Weill Cornell Medicine Qatar, Doha, Qatar

[3]Department of Obstetrics & Gynecology, Women's Wellness and Research Center, Doha, Qatar

[4]Clinical Department, College of Medicine, QU Health, Qatar University, Doha, Qatar

[5]University of Dundee, Dundee, UK

[6]Department of Radiology, PHCC, Doha, Qatar

[7]Department of Laboratory Medicine and Pathology, Hematology Division, Hamad Medical Corporation, Doha, Qatar

[8]Department of Radiology, Women's Wellness and Research Center, Doha, Qatar

Correspondence
Samah Kohla, Department of Lab Medicine and Pathology, Hematology Division, Hamad Medical Corporation, Al-Rayyan Street, Doha, 3050, Qatar.
Email: skohla@hamad.qa

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Abstract

Heterotopic pregnancy (HP) describes the simultaneous presence of two pregnancies at different implantation sites. Usually, one pregnancy is intrauterine and the other one is ectopic. The incidence of HP after assisted reproductive technologies reaches 1:3900, but is very rare after a spontaneous pregnancy, with a reported incidence of 1 to 30,000 pregnancies.

Due to its rarity, complex clinical picture, and laboratory findings, it is challenging to diagnose HP. We present a case of spontaneous HP diagnosed in the first trimester by ultrasound (US) and magnetic resonance imaging (MRI) and subsequently managed successfully. We present an analysis of the clinical and laboratory findings as well as imaging, including MRI that we used to diagnose the condition. Additionally, we performed a literature review.

Conclusions: HP is a very rare condition frequently faced in obstetrics, gynecology, and emergency departments that requires a high index of clinical suspicion. US remains the imaging modality of choice in diagnosing a HP, however, in some cases, an MRI with a reported safety in the first trimester, can be used to provide additional information over US.

KEYWORDS

ectopic tubal pregnancy, heterotopic pregnancy, heterotrophic pregnancy, pelvic MRI, transvaginal Ultrasound

1 | INTRODUCTION

Heterotopic (also called heterotrophic) pregnancy is the simultaneous occurrence of two pregnancies in two different implantation sites. Most of the time one of the pregnancies is intrauterine and the other is an ectopic pregnancy. HP is estimated to occur in 1 every 3900 pregnancies after assisted reproductive technologies (ART), reaching up to 1.5 in every

Abbreviations: ART, assisted reproductive technologies; β-hCG, beta human chorionic gonadotropin; HP, heterotopic pregnancy; MRI, magnetic resonance imaging; US, ultrasound.

1000 pregnancies.[1] In some studies, their reported incidence is as high as 1 in every 100 pregnancies after ART.[2–4] Although the true incidence of HP following ART is difficult to confirm, it is postulated that such an increased incidence in this cohort of patients, is related to previous tubal pathology, multiple ovulations or multiple embryo transfers.[2]

Following a spontaneous pregnancy however, the incidence of HP is rare. In a large review of the world's literature on combined intrauterine and extrauterine pregnancies, the reported incidence was 1 every 30,000 pregnancies.[4] Spontaneous HP – in particular – pose a real challenge for healthcare professionals not only in treatment but in diagnosis. This is is in part due to their rarity and unexpected occurrence. Ectopic pregnancies per se pose a diagnostic challenge on their own accord. HP will pose an even more diagnostic uncertainty; as seeing an intrauterine gestational sac may give false reassurance of an ongoing intrauterine pregnancy, and thus erroneously excluding the presence of an ectopic pregnancy.

Furthermore, β -human Chorionic gonadotrophins (β-hCG) serial measurements may not be useful in cases of HP due to the presence of two pregnancies in different locations.[5]

In our article, we present a case of spontaneous conception resulting in a HP. We provide a review of the diagnostic features, imaging, and management.

2 | CASE PRESENTATION

A 38-year-old gravida 5 para 4 woman presented to the emergency department with an increasing lower abdominal pain for 5 days, brownish vaginal discharge, nausea, and episodes of vomiting. She has a body mass index of 32 kg/m^2 and previously had 4 normal uncomplicated deliveries. The current pregnancy was a spontaneous conception, with no assistance. She had no previous history of relevance, no history of pelvic inflammatory disease, and was a non-smoker. She was not using any contraception. On presenting to our emergency, she was vitally stable and apart from some tenderness in both adnexa, the abdominal and vaginal clinical examination was unremarkable. Laboratory investigations revealed a serum β-hCG of 169,863 mIU/ml. Transvaginal ultrasound was performed using an endocavitary 5–9 MHz transducer. Grayscale ultrasound confirmed by color dopplers revealed a viable intrauterine pregnancy of 9 weeks and 5 days and a heterogeneous complex left adnexal mass suggestive of being a HP. The ovaries were unremarkable, and a small pelvic fluid collection was also seen. Doppler ultrasound of the described mass revealed a 'ring of fire' sign (Figure 1).

MRI imaging was done using a 1.5 T device (Siemens, Germany). A phased-array surface coil was centered over the abdomen to the symphysis pubis. Images were acquired from the level of the hepatic hilum to the symphysis pubis. The sequences included the turbo spin-echo (TSE) technique, gradient-echo (FLASH), and T1 and T2 weighting to obtain axial and coronal images. No contrast was given.

MRI study revealed a left adnexal rounded mass lesion (56 × 35 × 46 mm) intimately anterior to the normal left ovary, displaying a mixed hyper- and hypo-intense signal at T1 and T2 WI. It had a thick wall showing a high T2 signal (Figures 2–4). This increased our suspicion towards the presence of an ectopic pregnancy in the left tube.

After careful counseling and informed consent, the patient was taken to the operating theatre. Under general anesthesia, a laparoscopy was performed which revealed a distended left fallopian tube. The other (right) tube and both ovaries were unremarkable. A left salpingectomy was performed, and this was sent for histopathological assessment. The postoperative course was uneventful, and the patient was discharged home after confirming the viability of the intrauterine pregnancy by US.

Histopathological examination of the specimen showed a dilated congested segment of the left fallopian tube while

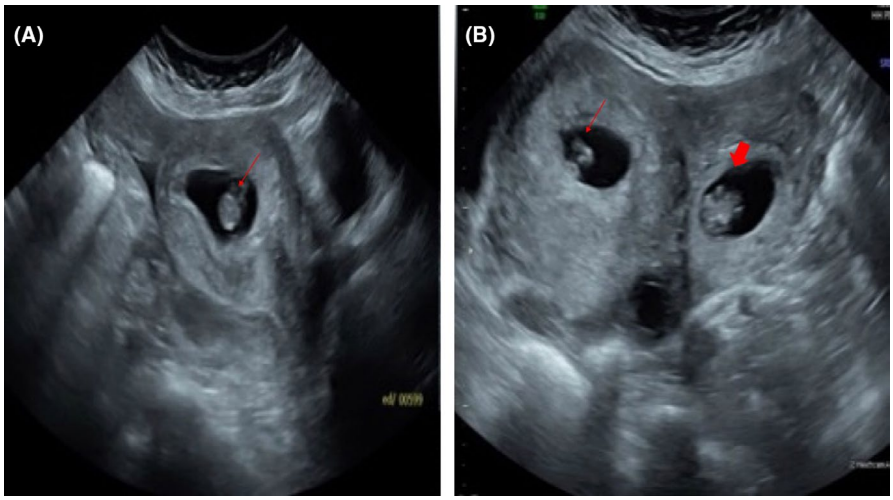

FIGURE 1 TVU: Intrauterine and ectopic pregnancy with an intraperitoneal fluid collection.

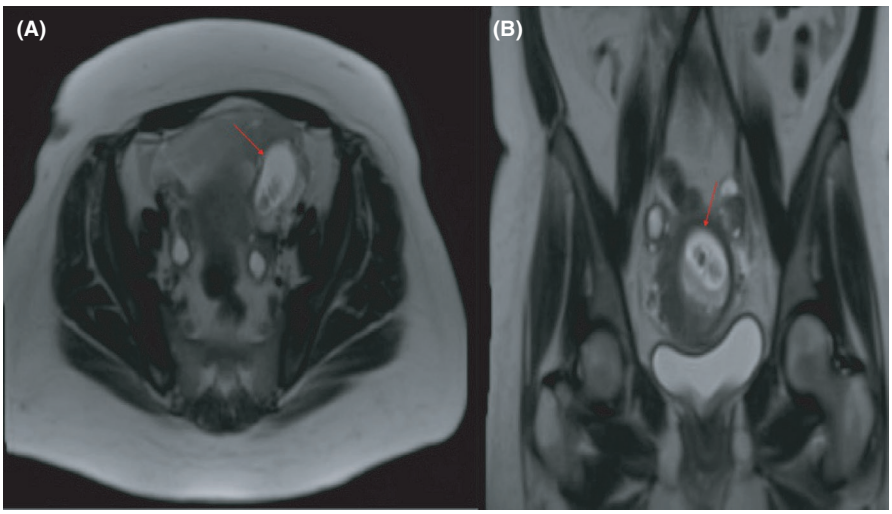

FIGURE 2 T2 Haste, axial and coronal, revealed left tubal ectopic pregnancy seen as a sac-like lesion with thick wall measures 56 x 35 x 46 mm contains fetus with crown-rump length 27 mm and intrauterine pregnancy with same crown-rump length.

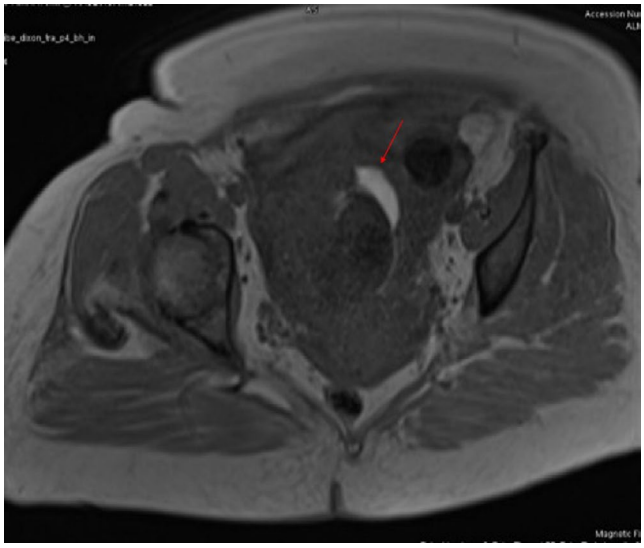

FIGURE 3 Axial T1 WI, Subchorionic hematoma as high signals.

microscopic examination revealed fragments of a blood clot, decidual tissue, and chorionic villi with trophoblasts noted within the dilated fallopian tube consistent with a tubal ectopic pregnancy.

3 | DISCUSSION

Ectopic pregnancy can be a life-threatening condition and still remains a cause of up to 4.9% of all maternal deaths in developed countries with almost 80% of all maternal deaths occurring during the first trimester of pregnancy.[6–8]

HP pregnancies can pose a difficult diagnostic challenge and a good number of women can present with serious clinical presentations as tubal rupture, acute abdomen, shock and hemoperitoneum.[5] Others may be asymptomatic and seeing an intrauterine pregnancy can add to the confusion, where presenting symptoms can be mistaken for a threatened miscarriage.[9]

The early diagnosis of an ectopic pregnancy is possible due to a combination of ultrasound and serum measurements β-hCG. A doubling time of serum β-hCG of 66% was initially used in the early 80s.[10] Following that a doubling time of 53%[11] and more recently 35% or more, over a 2 day period, was suggested.[12,13] Another concept in the early diagnosis of ectopic pregnancies is the discriminatory zone with levels 1500–2000 iu/ml,[14] or more recently a conservative level 3500 iu/ml was suggested.[15]

Unfortunately, in HP pregnancies, both concepts; the doubling time and discriminatory zones, commonly used in early diagnosis of ectopic pregnancy, are unlikely to be helpful, thus posing an increased risk of misdiagnosis, with a third to half of HP cases thus presenting late and have already ruptured before a diagnosis was made. In a review of the world literature on 589 combined intrauterine and extrauterine pregnancies, a combination of signs and symptoms including abdominal pain, peritoneal irritation and enlarged uterus were the most significant findings, with the pelvic inflammatory disease a significant risk factor.[4,5,16] The level of serum β-hCG in HP represents the combined contribution of both the intrauterine (mainly) and extrauterine pregnancy and are unlikely to be of clinical use for the diagnosis of a HP. Furthermore, visualizing both intrauterine and extrauterine fetal heart activity – although can be diagnostic – is unfortunately rare.[9]

To add to the diagnostic challenge, a HP can be misdiagnosed as a corpus luteum cyst, A helpful adjunct in such cases is using a Doppler ultrasound and visualising the 'ring of fire sign.[17] This is what we performed in our case.

Although ultrasound remains the main imaging modality in ectopic and HP pregnancies, a subset of patients may need further imaging using MRI to provide additional information.

In a review of 1737 patients exposed to first trimester MRI exposure, as compared with non-exposure, there was

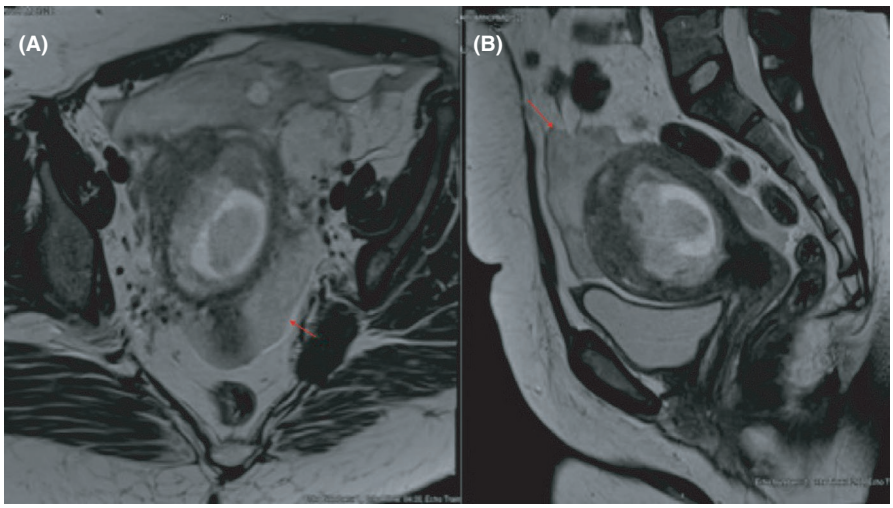

FIGURE 4 MRI T2 WI. Shows hemoperitoneum (clotted blood) as intermediate signals anterior and superior to the uterus.

no associated increased risk of harm to the foetus or in early childhood of up to 4 years of age, this includes the risk of stillbirth or neonatal death within 28 days of birth and any congenital anomaly, neoplasm, hearing and vision loss. In contrast, Gadolinium MRI during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions and for stillbirth and neonatal death.[18]

Ultrasound remains the imaging modality of choice in pregnancy. MRI – in selected patients, has another advantage due to its excellent soft-tissue contrast without the use of ionizing radiation. Findings on MRI include tubal dilation and wall enhancement, tubal hematoma, adnexal hematoma, and a gestational sac-like structure.[19] In our patient, an MRI revealed an adnexal rounded mass lesion with a thick wall showing a high T2 signal.

Any treatment for HP should aim to target the ectopic pregnancy, selectively, without harmful effects to the ongoing intrauterine pregnancy.

With this concept in mind, systemic methotrexate is contraindicated with a viable intrauterine pregnancy.[20] Local treatment modalities have thus been suggested to avoid the use of systemic agents in HP, and these include local injection of potassium chloride[21] and hyperosmolar glucose.[22]

Although local injections of these agents avoid surgery – at least initially – the risk of failure of such treatments and subsequent surgery and salpingectomy is high, reaching 55%, making them not an attractive in the context of HP with the other pregnancy in the tube.[23] These modalities, however, may have a place in ectopic pregnancies with no concomitant intrauterine pregnancy, scar pregnancies,[24,25] or in HP where the extrauterine sac is in an unusual location for example cervical or corneal.[26]

Realistic and practical approaches in HP with one of the pregnancies in the tube are performing a laparoscopy (preferred option) or laparotomy (depending on the clinical condition and expertise) and undertaking a salpingectomy (usually if the other tube is normal) or salpingotomy.[20] Another advantage of the surgical approach is that laparoscopy (or laparotomy) can confirm the diagnosis in addition to providing a definitive treatment.

Although salphingotomy has an established role in ectopic pregnancy, it's role in HP may not be similar for 2 reasons;

Firstly, there is a risk of around 21% of a repeat operation via salpingectomy due to persistent tubal bleeding[27] and this risk should not be taken lightly with a remaining ongoing intrauterine pregnancy.

Secondly, as opposed to salpingectomy, a salpingotomy carries the additional risk of persistent trophoblasts of around 7%[28] which is unlikely to be followed up by β-hCG due to the concurrent intrauterine pregnancy, nor treated with systemic methotrexate for the same reason.

We believe it is more appropriate to perform a salpingectomy rather than a salpingotomy in HP cases as it minimizes the risks that are inherently associated with salpingotomy, both during, and after the procedure.

4 | CONCLUSIONS

Heterotopic pregnancy is a very rare condition that requires a high index of clinical suspicion that may occasionally face health care professionals in obstetrics, gynaecology and emergency departments. It is even less common after a spontaneous conception. Although a high index of suspicion for ectopic pregnancy is now part and parcel of modern clinical practice, yet seeing an intrauterine pregnancy may give false reassurance, with a good number of heterotopic pregnancies potentially misdiagnosed and discovered at later stages after rupture of the ectopic arm of heterotopic pregnancy. We believe that cases like this one can play a small part to help keep that vigilance. Ultrasound remains the imaging modality of choice in diagnosing a heterotopic pregnancy, however, in carefully selected cases, an MRI with a reported safety in

the first trimester can be utilized and may provide added information over ultrasound. Salpingectomy rather than salpingotomy via laparoscopy should be the treatment of choice in most heterotopic pregnancies with the extrauterine pregnancy in the tube.

5 | DECLARATION

This manuscript is original work and has not been submitted and is not under consideration for publication elsewhere. All the authors have reviewed the manuscript and approved it before submission. Name of Department and Institution where this work was completed: Department of Radiology, Women's Wellness and Research Center, Hamad Medical Corporation, Doha, Qatar.

6 | CONSENT FOR PUBLICATION

Written informed consent of patient information, images for publication was signed by the patient before the submission of this manuscript.

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CONFLICT OF INTEREST

None declared.

AUTHORS CONTRIBUTIONS

Dr. Ahmed H. Abdelmonem and Dr. Gamal Sayed wrote and edited the manuscript. Dr. Reda Youssef wrote and edited the radiological part of the manuscript. Dr Abd Elwahid Abugazia and Dr. Samah Kohla reviewed and edited the manuscript.

ETHICS APPROVAL

The case report was approved by the Medical Research Centre at Hamad Medical Corporation, Qatar, and the Clinical Imaging Research Committee (CIRC).

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Samah Kohla https://orcid.org/0000-0002-1050-9922

REFERENCES

1. Clayton HB, Schieve LA, Peterson HB, Jamieson DJ, Reynolds MA, Wright VC. A comparison of heterotopic and intrauterine-only pregnancy outcomes after assisted reproductive technologies in the United States from 1999 to 2002. *Fertil Steril*. 2007;87(2):303–309.
2. Tal J, Haddad S, Gordon N, Timor-Tritsch I. Heterotopic pregnancy after ovulation induction and assisted reproductive technologies: a literature review from 1971 to 1993. *Fertil Steril*. 1996;66(1):1–12. https://doi.org/10.1016/s0015-0282(16)58378-2
3. Chin HY, Chen FP, Wang CJ, Shui LT, Liu YH, Soong YK. Heterotopic pregnancy after in-vitro fertilization–embryo transfer. *Int J Gynecol Obstet*. 2004;86:411–416.
4. Reece EA, Petrie RH, Sirmans MF, Finster M, Todd WD. Combined intrauterine and extrauterine gestations: a review. *Am J Obstet Gynecol*. 1983;146(3):323–330. https://doi.org/10.1016/0002-9378(83)90755-x
5. Basile F, Di Cesare C, Quagliozzi L, Donati L, Bracaglia M, Caruso A. Spontaneous heterotopic pregnancy, simultaneous ovarian, and intrauterine: a case report. *Case Rep Obstet Gynecol*. 2012;2012:509694.
6. Sindos M, Togia A, Sergentanis TN, et al. Ruptured ectopic pregnancy: risk factors for a life-threatening condition. *Arch Gynecol Obstett*. 2009;279:621–623.
7. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet*. 2006;367(9516):1066–1074.
8. Rocha Filho EA, Santana DS, Cecatti JG, et al. Awareness about a Life-threatening condition: ectopic pregnancy in a network for surveillance of severe maternal morbidity in Brazil. *Biomed Res Int*. 2014;2014:965724.
9. Soares C, Mações A, Novais Veiga M, Osório M. Early diagnosis of spontaneous heterotopic pregnancy successfully treated with laparoscopic surgery. *BMJ Case Rep*. 2020;13(11):e239423. https://doi.org/10.1136/bcr-2020-239423
10. Kadar N, Caldwell BV, Romero R. A method of screening for ectopic pregnancy and its indications. *Obstet Gynecol*. 1981;58:162–166.
11. Barnhart KT, Sammel MD, Rinaudo PF, Zhou L, Hummel AC, Guo W. Symptomatic patients with an early viable intrauterine pregnancy: HCG curves redefined. *Obstet Gynecol*. 2004;104:50-55.
12. Seeber BE, Sammel MD, Guo W, Zhou L, Hummel A, Barnhart KT. Application of redefined human chorionic gonadotropin curves for the diagnosis of women at risk for ectopic pregnancy. *Fertil Steril*. 2006;86:454-459.
13. Barnhart KT, Guo W, Cary MS, et al. Differences in serum human chorionic gonadotropin rise in early pregnancy by race and value at presentation. *Obstet Gynecol*. 2016;128(3):504-511. https://doi.org/10.1097/AOG.0000000000001568
14. Mehta TS, Levine D, Beckwith B. Treatment of ectopic pregnancy: Is a human chorionic gonadotropin level of 2,000 mIU/mL a reasonable threshold? *Radiology*. 1997;205:569-573.
15. Connolly A, Ryan DH, Stuebe AM, Wolfe HM. Reevaluation of discriminatory and threshold levels for serum β-hCG in early pregnancy. *Obstet Gynecol*. 2013;121(1):65-70. https://doi.org/10.1097/aog.0b013e318278f421
16. Tal J, Haddad S, Gordon N, Timor-Tritsch I. Heterotopic pregnancy after ovulation induction and assisted reproductive

technologies: a literature review from 1971 to 1993. *Fertil Steril*. 1996;66:1-12.
17. Lin EP, Bhatt S, Dogra VS. Diagnostic clues to ectopic pregnancy. *Radiographics*. 2008;28(6):1661-1671. https://doi.org/10.1148/rg.286085506
18. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between mri exposure during pregnancy and fetal and childhood outcomes. *JAMA*. 2016;316(9):952-961. https://doi.org/10.1001/jama.2016.12126
19. Kataoka ML, Togashi K, Kobayashi H, Inoue T, Fujii S, Konishi J. Evaluation of ectopic pregnancy by magnetic resonance imaging. *Hum Reprod*. 1999;14(10):2644-2650. https://doi.org/10.1093/humrep/14.10.2644
20. Hutchinson M, Chan C. Laparoscopic management of ruptured heterotopic pregnancy after intrauterine insemination. *CMA J*. 2016;188(17-18):E525-E527. https://doi.org/10.1503/cmaj.160110
21. Salomon LJ, Fernandez H, Chauveaud A, Doumerc S, Frydman R. Successful management of a heterotopic caesarean scar pregnancy: potassium chloride injection with preservation of the intrauterine gestation: case report. *Hum Reprod*. 2003;18(1):189-191.
22. Goldberg Jeffrey M, Bedaiwy Mohamed A. Transvaginal Local Injection of hyperosmolar glucose for the treatment of heterotopic pregnancies. *Obstet Gynecol*. 2006;107(Supplement):509-510. https://doi.org/10.1097/01.AOG.0000187947.71490.d1
23. Goldstein JS, Ratts VS, Philpott T, Dahan MH. Risk of surgery after use of potassium chloride for treatment of tubal heterotopic pregnancy. *Obstet Gynecol*. 2006;107(Supplement):506-508. https://doi.org/10.1097/01.AOG.0000175145.23512.5e
24. Timor-Tritsch IE, Khatib N, Monteagudo A, Ramos J, Berg R, Kovács S. Cesarean scar pregnancies: experience of 60 cases. *J Ultrasound Med*. 2015;34(4):601-610. https://doi.org/10.7863/ultra.34.4.601
25. Li Q, Xu H, Wang Y, Liu Q, He P, Wang L. Ultrasound-guided local methotrexate treatment for cesarean scar pregnancy in the first trimester: 12 years of single-center experience in China. *Eur J Obstet Gynecol Reprod Biol*. 2019;243:162-167. https://doi.org/10.1016/j.ejogrb.2019.10.036
26. Doubilet PM, Benson CB, Frates MC, Ginsburg E. Sonographically guided minimally invasive treatment of unusual ectopic pregnancies. *J Ultrasound Med*. 2004;23(3):359-370. https://doi.org/10.7863/jum.2004.23.3.359
27. Mol F, van Mello NM, Strandell A, et al. European Surgery in Ectopic Pregnancy (ESEP) study group. Salpingotomy versus salpingectomy in women with tubal pregnancy (ESEP study): an open-label, multicentre, randomised controlled trial. *Lancet*. 2014;383(9927):1483-1489. https://doi.org/10.1016/S0140-6736(14)60123-9
28. Fernandez H, Capmas P, Lucot JP, Resch B, Panel P, Bouyer J; GROG. Fertility after ectopic pregnancy: the DEMETER randomized trial. *Hum Reprod*. 2013;28(5):1247-1253. https://doi.org/10.1093/humrep/det037

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