Heterotopic pregnancy: a report of two cases

Abstract

Background: A heterotopic pregnancy is defined as the presence of a concomitant intrauterine and extra-uterine pregnancy. Its estimated incidence is 1/30,000 in spontaneous pregnancies. It is also reported to be as high as 1 in 3900 when the pregnancy is a result of assisted reproductive technology (ART). However, clomiphene citrate (CC) could be associated with a higher rate of heterotopic pregnancy as it amplifies the rate of twinning. Furthermore, heterotopic pregnancies are a diagnostic and therapeutic challenge for obstetricians. If undiagnosed, they are associated with significant maternal morbidity and mortality.

Case presentation: We present two cases of coincidental intra and extra-uterine pregnancy. In the first case, heterotopic pregnancy was a result of induction of ovulation with CC. There was a delay in the diagnosis of the ectopic pregnancy component resulting in an emergency laparoscopy. Fortunately, after the laparoscopy the intrauterine pregnancy was not affected and it is progressing satisfactorily. Alternatively, the second case occurred spontaneously and was treated with methotrexate as the intrauterine pregnancy miscarried on its own accord.

Conclusions: These cases highlight the fact that as clinicians, we should be aware of the possibility of a heterotopic pregnancy in any patient presenting with pelvic pain, even when an intrauterine pregnancy has been confirmed. This is even more imperative after induction of ovulation by CC or ART. We would also like to emphasise that an early diagnosis is critical to safeguard the intrauterine pregnancy and avoid maternal morbidity and mortality due to the ectopic pregnancy.

Keywords: clomiphene citrate, ectopic, heterotopic pregnancy.

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Introduction

Heterotopic pregnancy (HTP) refers to the presence of simultaneous pregnancies at two different implantation sites,[1,2] most commonly, an intra-uterine and an ectopic. Of ectopic pregnancies (EP), 90% occur in the fallopian tube.[3] The incidence of heterotopic pregnancy is estimated to be 1/30,000 in spontaneous pregnancy but much higher (1/3900)[4,5] when associated with assisted reproductive technology (ART), including intrauterine insemination (IUI), super ovulation and in vitro fertilisation (IVF). According to more recent literature, clomiphene citrate (CC) could be related to a higher incidence of HTP as it increases the rate of twinning.[6] This rare obstetric condition carries considerable maternal morbidity and mortality as a result of the risk of ruptured EP.[7] Besides the difficulty in diagnosing HTP, management can be difficult and the condition may be life threatening; even when surgical intervention is performed. Therefore, taking a thorough history is critical to identify HTP risk factors (Table 1 and 2).

The first case study describes a ruptured tubal HTP in a patient who became pregnant with the aid of CC. She presented at six weeks gestation and was treated with an immediate laparoscopy. She recently delivered at 40 weeks by normal vaginal delivery and had a female child weighing 3500 g.

The second case study describes a spontaneously conceived cornual HTP. She also presented at six weeks of gestation and was treated with high dose methotrexate (MTX) as the intrauterine pregnancy miscarried by itself. This would have posed a management dilemma, however the intrauterine pregnancy miscarried on it's own and the HTP was treated by MTX.

Case presentation

A 33-year-old multiparous Caucasian woman initially presented to the emergency department (ED) with a one-week history of amenorrhea, mild lower abdominal pain and vaginal spotting. She had taken CC due to a history of polycystic ovary syndrome (PCOS). Her vital signs were stable and her examination was unremarkable. Blood tests revealed haemoglobin (Hb) of 150 g/L with a positive beta-human chorionic gonadotrophin (BHCG) of 2400 IU/L, and an O negative blood group. Ultrasound scan (USS) confirmed an intra-uterine gestational sac of 3.5 mm (5 weeks gestation) with two 20 mm right ovarian cysts. Also some free fluid was reported in the pelvic cavity.

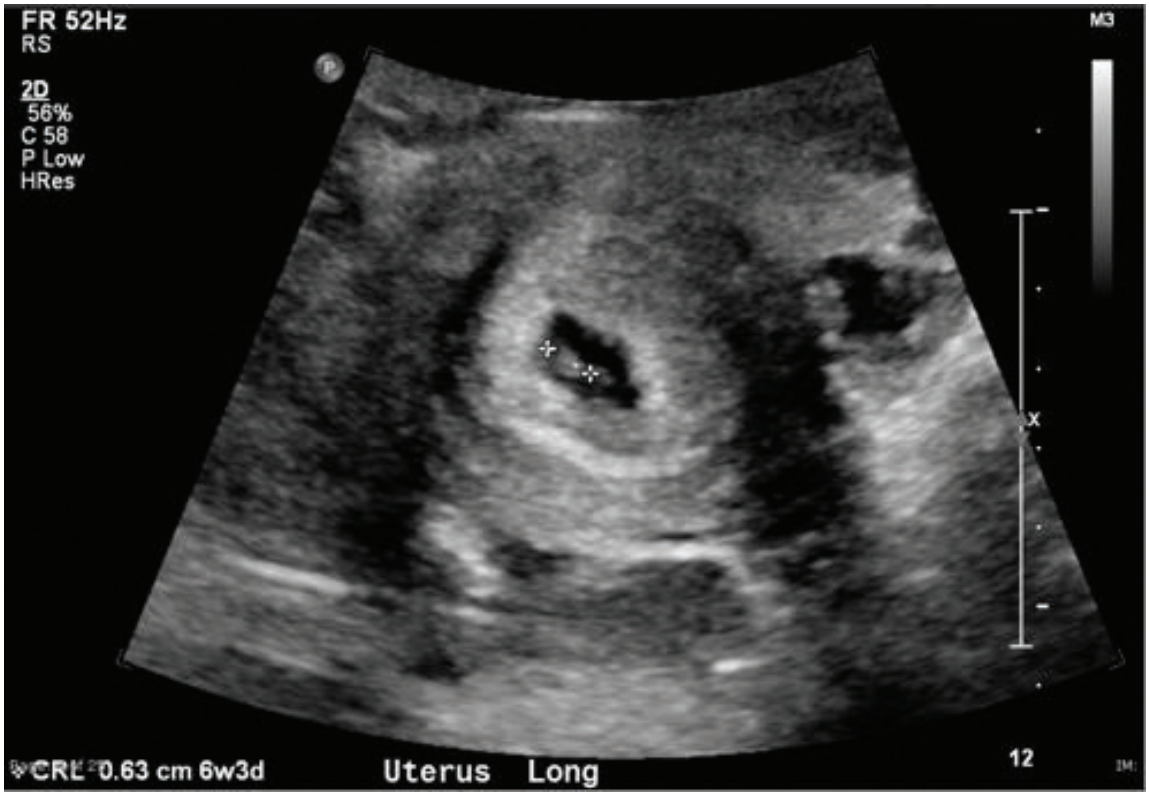

Figure 1: Live intra uterine pregnancy of a Crown-Rump Length (CRL) of 6.3 mm (6 weeks and 3 days).

Table 1: Risk factors ectopic pregnancy.

Degree of risk	Risk factors	Odds ratio
High	Previous ectopic pregnancy	9.3–47
	Previous tubal surgery	6.0–11.5
	Tubal ligation	3.0–139
	Tubal pathology	3.5–25
	In utero DES exposure	2.4–13
	Current IUD use	1.1–45
Moderate	Infertility	1.1–28
	Previous cervicitis (gonorrhea, chlamydia)	2.8–3.7
	History of pelvic inflammatory disease	2.1–3.0
	Multiple sexual partners	1.4–4.8
	Smoking	2.3–3.9
Low	Low Previous pelvic/abdominal surgery	0.93–3.8
	Vaginal douching	1.1–3.1
	Early age of intercourse (<18 years)	1.1–2.5

Adapted from data in Ankum, WM, Mol, BWJ, Van Der Veen, F, Bossuyt, PMM. *Fertil Steril* 1996; 65:1093 and Murray, H, Baakdah, H, Bardell, T, Tulandi, T. *CMAJ* 2005; 173:905 and Bouyer, J, Coste, J, Shojaei, T, *et al. Am J Epidemiol* 2003; 157: 185.

Table 2: Risk factors HTP.

Risk factors	Incidence rate
ART	1/100 to 1/3900
Tubal damage: Surgeries or Endometriosis[8]	6 folds more
Pharmacological ovulation induction	33/10000
Ectopic pregnancy	–
Pelvic inflammatory disease	–
Previous EP[9]	–

As a result, she was discharged after Anti D was given and referred to the early pregnancy assessment unit (EPAU) for observation and further management with advice to return if pain or bleeding worsened.

She represented to the emergency department (ED) 12 days later, complaining of aggravating severe colicky left iliac fossa pain, associated with minimal vaginal (PV) bleeding and vomiting. She was alert and oriented and her observations were stable. Apart from some mild tenderness in the left lumbar region and right renal angle, her examination was unremarkable. Correspondingly, her blood tests showed a βHCG of 34,000 IU/L with a drop in her Hb level to 120 g/L. An ultrasound scan was requested to check fetal viability and to exclude any renal pathology. The ultrasound demonstrated a live intra-uterine pregnancy of a crown-rump length (CRL) of 6.3 mm (6 weeks and 3 days) (Figure 1) and a foetal heart rate (FHR) of 118 bpm (Figure 2) with a large amount of free fluid in abdomen (Figures 3, 4 and 5).

These findings demonstrated a simultaneous intra-uterine pregnancy (IUP) and a ruptured tubal ectopic. The differential diagnosis was that of an IUP with a ruptured ovarian cyst. She required resuscitation with two units of packed red blood cells. Furthermore, an emergency laparoscopy was performed under general anesthesia which revealed a 2.5 L hemo-peritoneum of old blood and clots with a ruptured left tubal ectopic. Consequently, a left salpingectomy was performed. The histological examination confirmed a ruptured left tubal ectopic pregnancy.

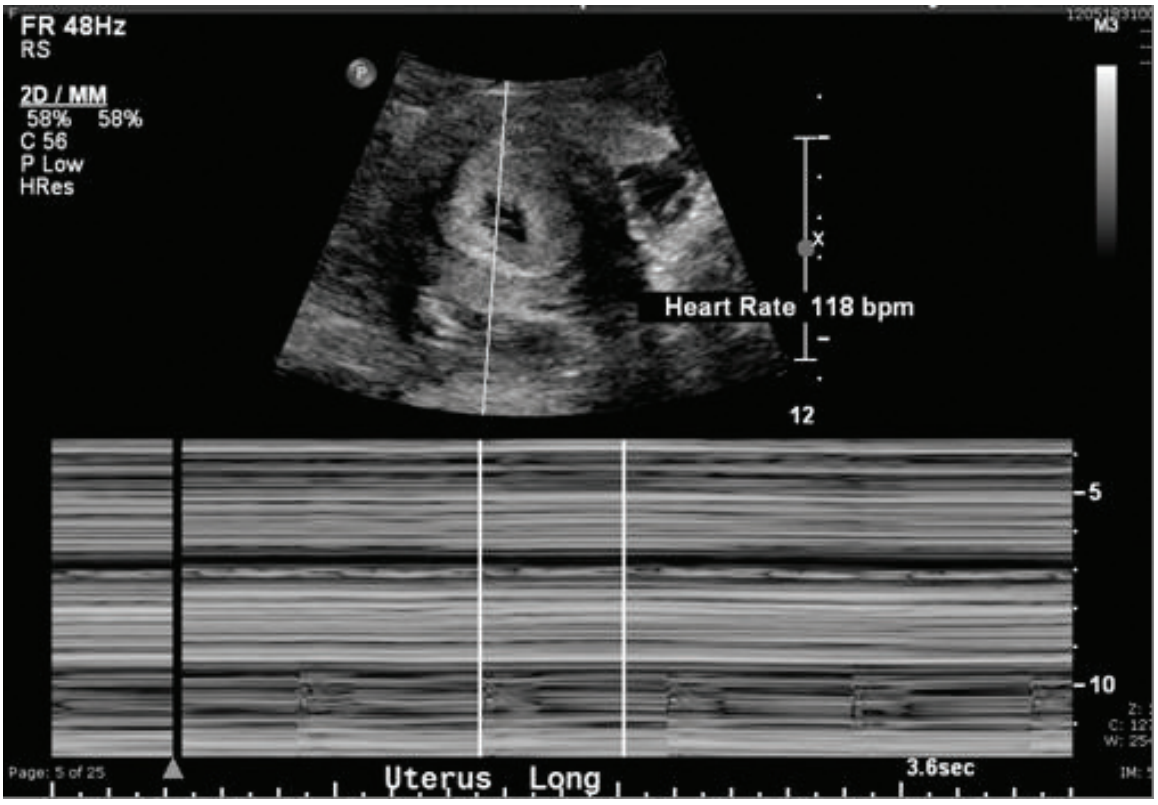

Figure 2: Foetal Heart Rate (FHR) of 118 bpm.

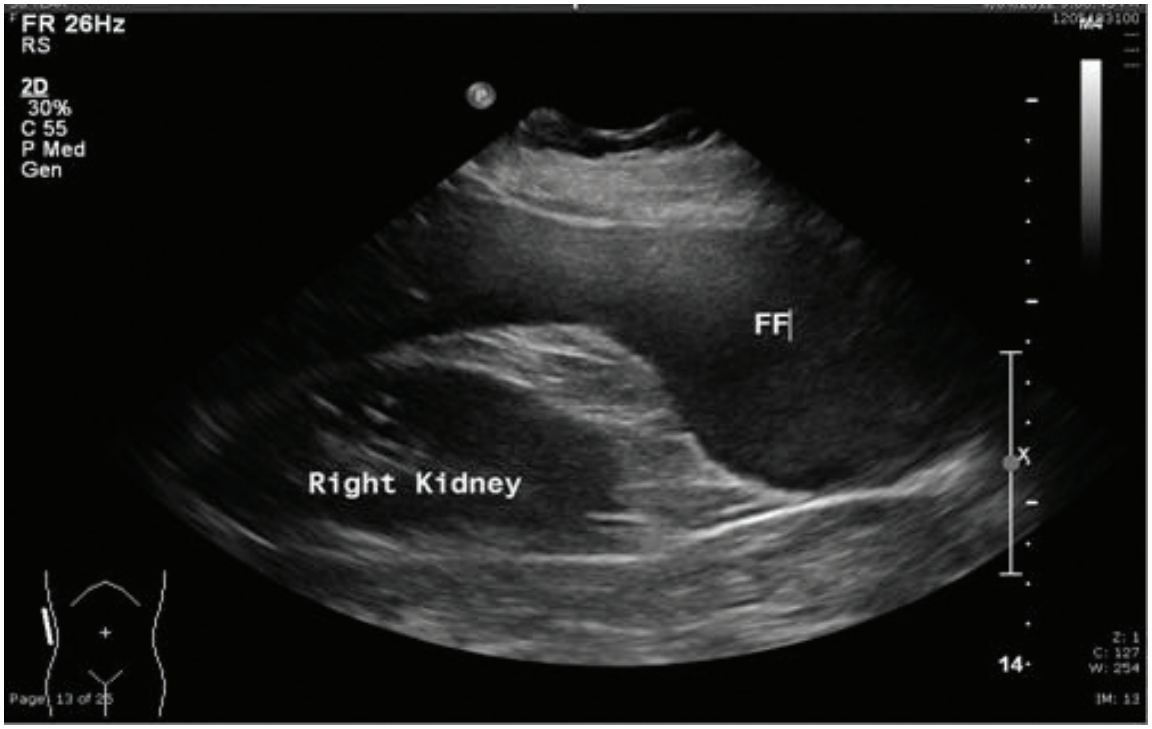

Figure 3: A large amount of free fluid in abdomen.

She recovered well postoperatively and was discharged two days after the procedure. A week after surgery, a live IUP with a CRL equivalent to 9 weeks gestation was visualised on transabdominal ultrasound (Figure 6). The pregnancy continued uneventfully and she delivered a well, female child weighing 3500 g at 40 weeks.

Second case is of a 34-year-old woman who was initially presented to her general practitioner (GP) at 6 weeks gestation complaining of spotting and mild abdominal pain. She had no significant previous medical conditions and was not taking any medication. Her β-HCG was 9700 IU/L and USS revealed a possible cornual ectopic pregnancy. On admission to the hospital, her vital signs were stable and her examination was within normal limits. As the vaginal bleeding and abdominal

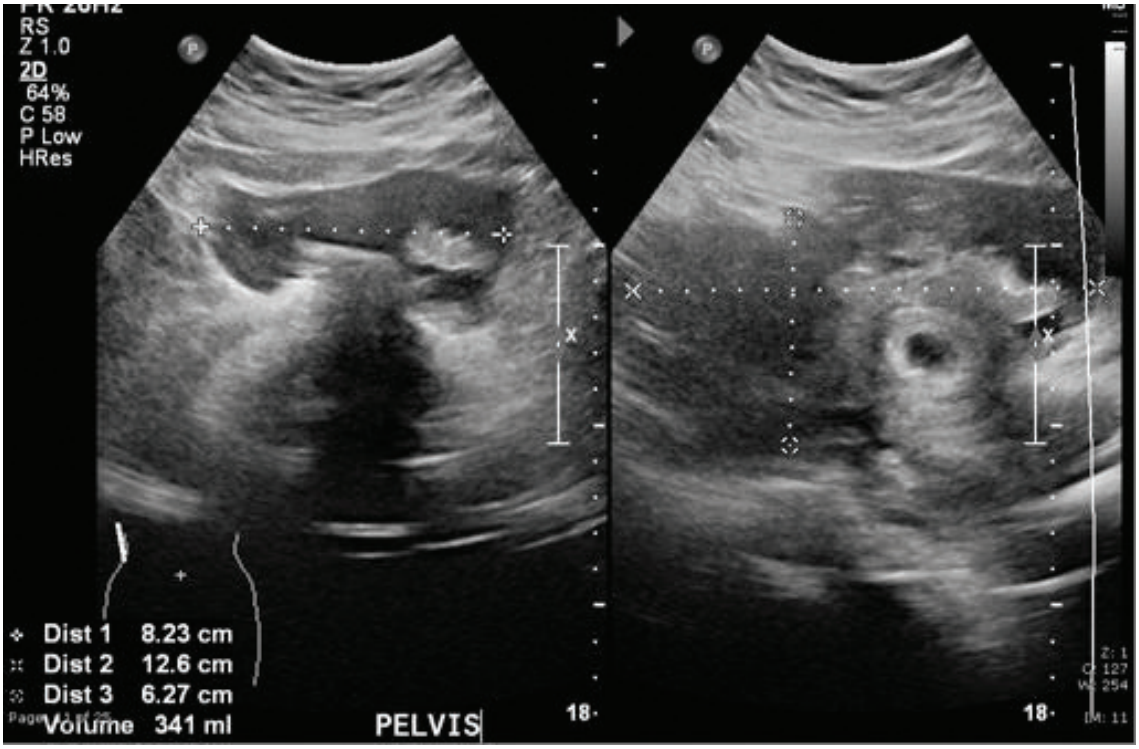

Figure 4: A large amount of free fluid in abdomen.

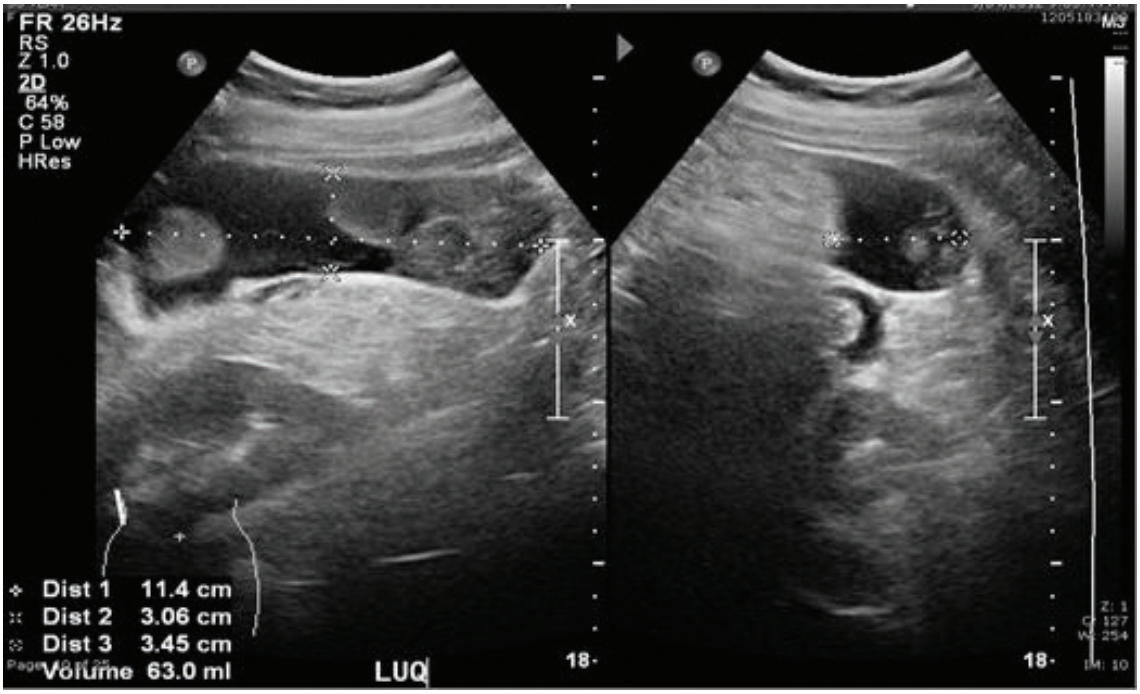

Figure 5: A large amount of free fluid in abdomen.

pain settled, she was discharged the following day with advice to represent to early pregnancy assessment unit (EPAU) for further β-HCG and USS.

Her βHCG continued to rise to 36000 IU/L and the second USS revealed an intrauterine centrally located intrauterine gestational sac, which contained a 22 mm fetus (8 weeks 5 days gestation), with no heart beat.

There was also a second irregular mixed area of echogenicity in the right cornu of the uterus, which measured approximately 31 mm (9 weeks 6 days gestation) (Figures 7, 8 and 9).

The impression was that of a non viable intrauterine pregnancy with a right cornual heterotopic pregnancy. The patient was treated with Methotrexate. Her follow up USS a couple of weeks after treatment was normal.

Discussion

Duverney first described HTP in 1708.[10,11] Presently, the use of ART and fertility agents such as CC can increase a patient's risk

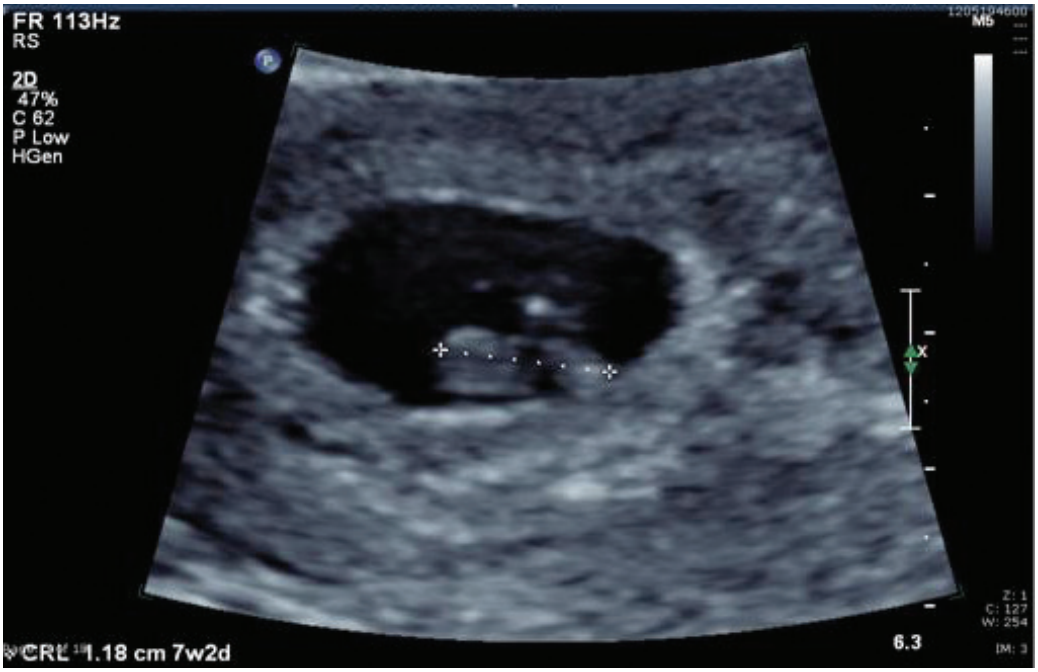

Figure 6: A week after surgery, a live IUP with a CRL equivalent to 9 weeks gestation was visualised on transabdominal ultrasound.

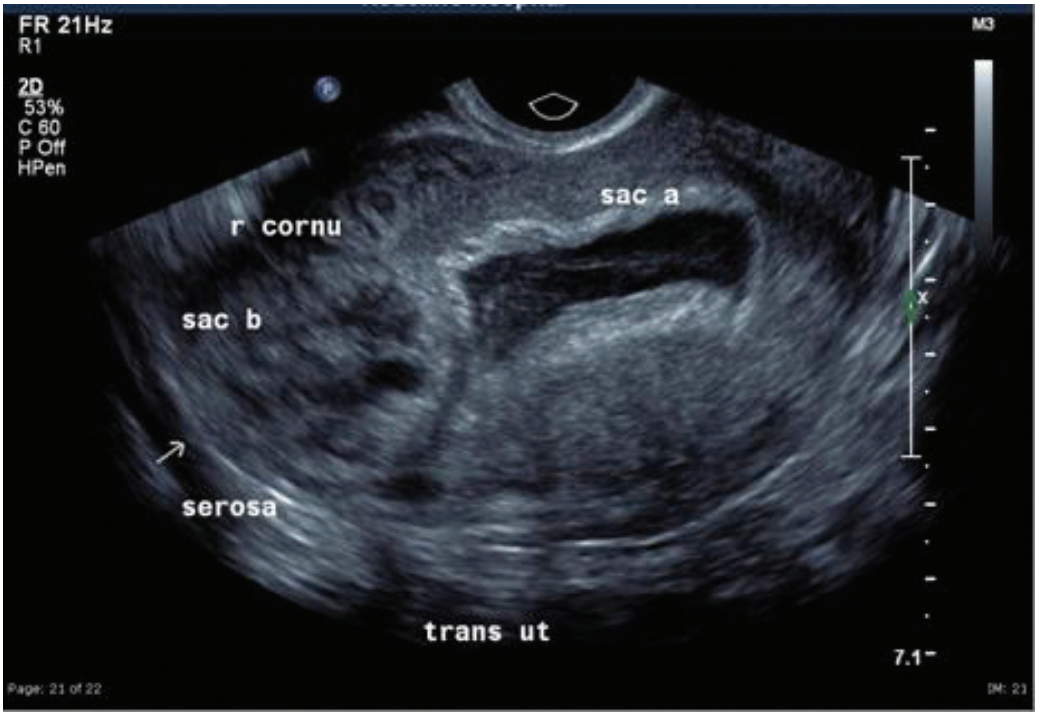

Figure 7: There was also a second irregular mixed area of echogenicity in the right cornu of the uterus, which measured approximately 31 mm (9 weeks 6 days gestation).

of HTP. This is possibly due to the combined effects of presence of tubal disease, high level of oestradiol and progestrone with hyperstimulation and the subsequent simultaneous transfer of several embryos into the uterus with retrograde flow into the fallopian tubes.[10,12]

Indeed, any factor predisposing a patient to an increased risk of ectopic pregnancy (EP) and/or multiple pregnancies can contribute to HTP.[10,11,13,14] In our patient (case 1), pregnancy also occurred in association with ovulation induction by CC.

Spontaneous HTP has an incidence of approximately 1 in 39,000. Most of the HTP cases are diagnosed late, resulting in significant morbidity and occasional mortality.[10] As no single investigation can predict the presence of a HTP, it should be suspected in any patient, presenting with lower abdominal pain in the early phase of an obvious IUP following fertility treatment[11,15].

Often, abdominal and pelvic USS fail to show an ectopic pregnancy or the ultrasound is misinterpreted because of the awareness of an existing IUP.[10,14] Demonstration of an IUP is not a reliable indicator for excluding an ectopic pregnancy.[10,12]

EP is normally visualised on USS in three forms including "blob" sign, "bagel" (doughnut) sign or a gestational sac with a fetal pole.[16] But most USS reports make no comment of a search for coexistent ectopic pregnancy when assessing an intrauterine

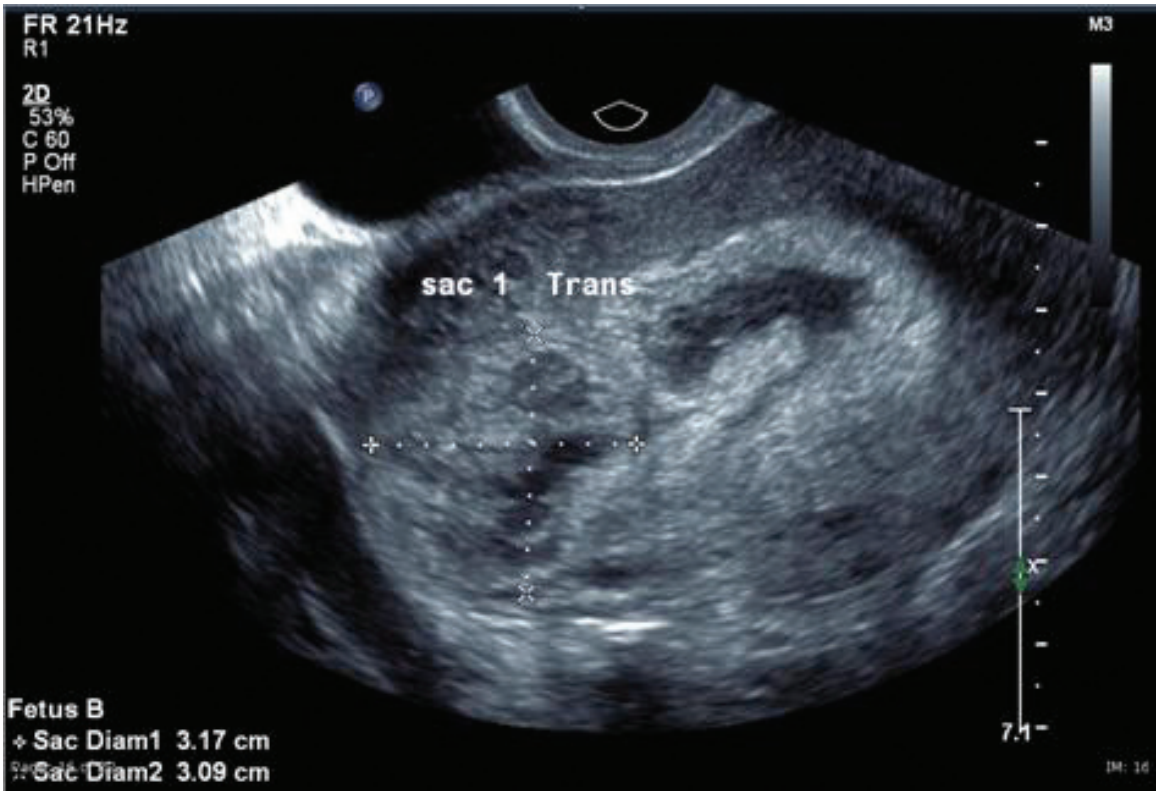

Figure 8: There was also a second irregular mixed area of echogenicity in the right cornu of the uterus, which measured approximately 31 mm (9 weeks 6 days gestation).

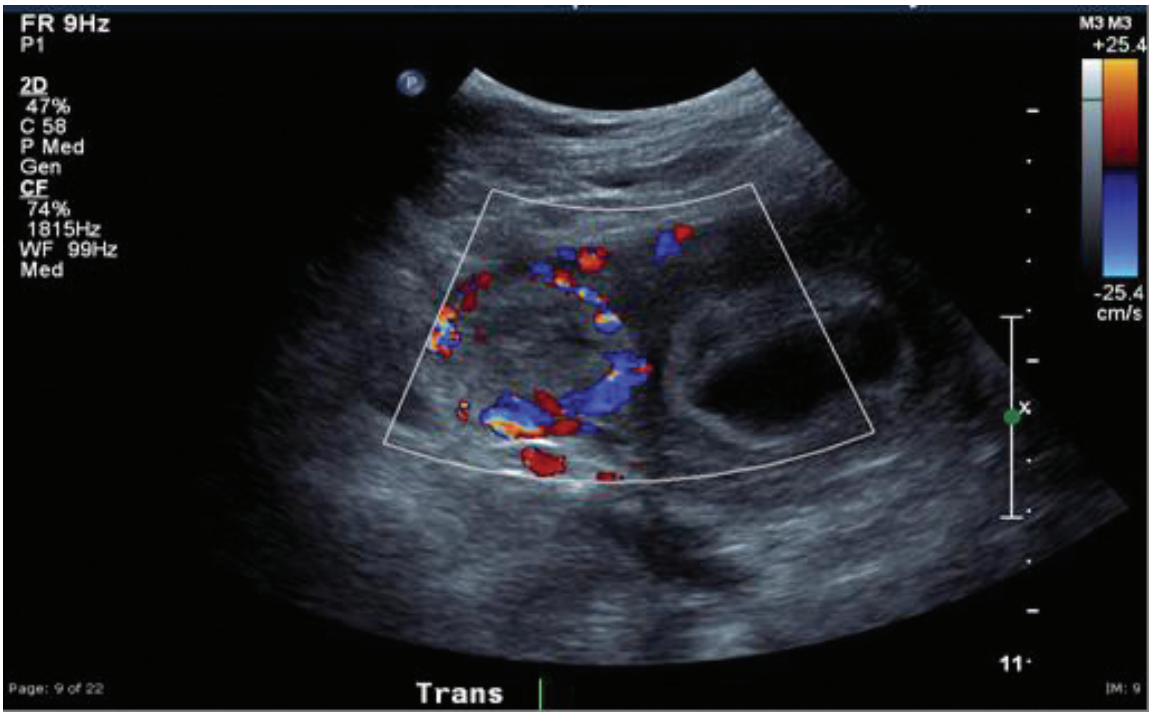

Figure 9: There was also a second irregular mixed area of echogenicity in the right cornu of the uterus, which measured approximately 31 mm (9 weeks 6 days gestation).

gestation, because a HTP is still thought to be tremendously rare. For this reason, almost all EPs are diagnosed by excluding an IUP.[13]

The first patient presented early in the pregnancy with a history of minimal vaginal bleeding and lower abdominal pain, which are both common symptoms of IUP. There was also a delay in the diagnosis of the EP component and as its presence was not identified until an EP rupture had occurred and the patient developed a significant hemoperitoneum. Although the primary USS confirmed the presence of an IUP, it failed to identify the EP.

The management of HTP remains controversial. Surgical therapy has been the traditional mainstay but involves surgical and anaesthetic risks to both the mother and IUP.[14] Treatment should be modified to the site of implantation and the least invasive treatment should be considered in order to preserve the concomitant pregnancy. Studies suggest that laparoscopic

management is preferred over laparotomy in patients with a suspected EP, alongside a documented IUP because of minimal manipulation of the uterus. Therefore, laparoscopic salpingectomy is the standard approach and is the first line of treatment in the setting of a ruptured EP.[11]

A non-surgical approach may be used safely and effectively to manage patients who are clinically stable and where a HTP is recognised relatively early in gestation. A successful non-surgical management of six cases of HTP using potassium chloride (KCl) injection into the tubal EP has been reported.[14]

Conclusions

We reiterate that HTP must always be considered in all patients presenting with abdominal or pelvic pain in the presence of a documented IUP. This is because the presence of an IUP does not always exclude the presence of a HTP. It is important to assess the patient for a coexisting EP, contributing to the symptoms. Thus, we recommend that all patients, especially those who are symptomatic, must be assessed comprehensively to exclude the presence of a simultaneous HTP. We also emphasise the need for prompt and immediate action when a HTP is suspected, to avoid missing this potentially life-threatening condition.

Consent

Verbal informed consent was obtained from both patients for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AK contributed to the interpretation of Ultrasound scans. AK and SF compiled and approved the final manuscript and ultrasound images.

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