

## CASE REPORT

# Ectopic pregnancy of the fundal myometrium in a patient with tuberous sclerosis

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**Abstract**

A myometrial ectopic pregnancy is a rare and potentially fatal diagnosis. This diagnosis should be considered when presented with large increases in serum beta-hCG with no evidence of an intrauterine pregnancy, particularly with altered myometrium.

**KEYWORDS**

acute medicine, general surgery, genetics, obstetrics and gynaecology

## 1 | BACKGROUND

This case report outlines the challenging diagnosis and management of an intramyometrial ectopic pregnancy in the setting of tuberous sclerosis. A myometrial ectopic pregnancy is a rare diagnosis, occurring in less than 1% of all ectopic pregnancies. This diagnosis should be kept in mind when presented with large increases in serum beta-hCG with no evidence of an intrauterine pregnancy, particularly when a patient presents with a comorbidity that can alter the myometrium such as in tuberous sclerosis.

Ectopic pregnancies are the implantation of blastocysts in areas other than within the uterine cavity constituting approximately 2% of all reported pregnancies.<sup>1</sup> Among this percentage, nearly 95% are found within the fallopian tubes, and the other 5% within the ovary, cervix, peritoneal cavity, or prior cesarean scar. Intramyometrial pregnancy is the rarest of the ectopic pregnancies and less than 50 cases have been reported in literature.<sup>2</sup> It is estimated to occur in less than 1% of all ectopic pregnancies.<sup>3</sup> Intramyometrial pregnancy is defined as a pregnancy located within the uterine wall, completely surrounded by myometrium, and separated from the uterine cavity or fallopian tubes.<sup>3</sup> These gestations may be life-threatening, hence early detection is imperative to prevent complications and preserve future fertility.<sup>4</sup> The etiology of intramyometrial ectopic pregnancies is unclear, but many

investigators attribute it to sinus tracts within the endometrium caused by trauma, prior uterine surgery (dilation and curettage, cesarean section, myomectomy, manual removal of placenta), manipulation of the uterus, adenomyosis, or difficulty with assisted reproductive technology creating a false passage.<sup>5</sup>

In this case presentation, our patient did not have any of the aforementioned risk factors, however, her medical history was significant for Tuberous Sclerosis which we believe may have contributed to the development of an intramyometrial ectopic pregnancy. We herein report her hospital course and summarize current data regarding etiology, diagnosis, investigation, and optimal treatment from our experience.

## 2 | CASE PRESENTATION

A 30-year-old woman gravida 2, para 0 first became known to the gynecology team while inpatient under the internal medicine service for treatment of pneumothorax. The patient had a known history of tuberous sclerosis and had a left-sided chest tube in place awaiting pleurodesis. However, on the day of the procedure, a mandatory preprocedural positive urine pregnancy prompted a gynecology consult and procedure cancellation.

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At the time of consultation, the patient denied any abdominal pain or vaginal bleeding and was 6.6 weeks by her last menstrual period. She had a history of one previous first-trimester termination of pregnancy without a dilatation and curettage, as well as a known diagnosis of polycystic ovarian syndrome on metformin. The patient's beta-hCG on hospital day 7 was 2578 mIU/mL and a transvaginal ultrasound performed the following day could not identify an intrauterine gestational sac. She was diagnosed with a pregnancy of unknown location with a recommendation of a repeat beta-hCG and transvaginal ultrasound. Upon repeat testing 48 hours following initial consultation, the patient's beta-hCG increased by 95% to 5028 mIU/mL. Transvaginal ultrasound again could not identify an intrauterine gestational sac but did present a  $1.64 \times 1.32$  cm hypoechoic structure in the fundal myometrium just left of the midline with surrounding vascularity (Figure 1). As no definite ectopic pregnancy was identified at that time and the patient was asymptomatic in the setting of a highly desired pregnancy, the decision was made to repeat beta-hCG and imaging in another 48 hours.

The patient's beta-hCG continued to rise an additional 56% to 7850 mIU/mL 48 hours after the previous value and was 9335 mIU/mL (19% increase) on the day of repeat transvaginal ultrasound. The imaging remained unchanged except for a new finding of a small amount of pelvic free fluid. The fundal hypoechoic lesion was once again demonstrated and was now classified as a fibroid versus an interstitial ectopic pregnancy (Figure 2). The patient continued to deny any abdominal pain or vaginal bleeding, and her abdominal exam remained benign. At this time, the patient was counseled extensively by the gynecology team on likely interstitial versus cornual ectopic pregnancy, and the need for medical versus surgical intervention.

Along with the management of a pregnancy of unknown location, the patient was simultaneously managed for persistent pneumothorax by a multidisciplinary team including internal medicine, pulmonology, and cardiothoracic surgery. Removal of her left-sided chest tube had been unsuccessful and the patient remained on continuous chest tube suction. Given her comorbidities, the decision was made to attempt methotrexate therapy, although surgical management had

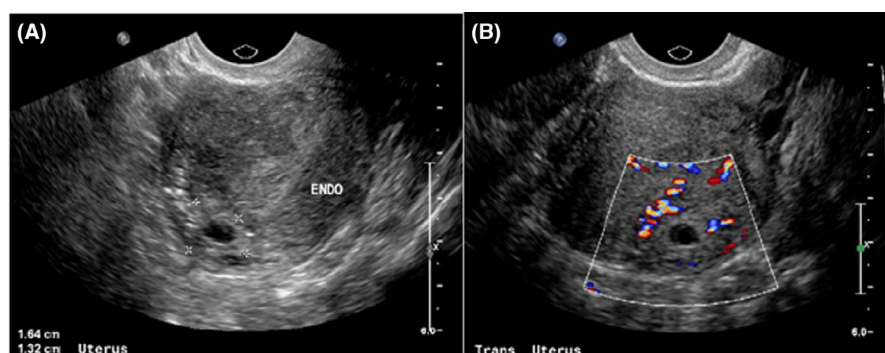
been the desired route at the time. Pulmonary toxicity due to methotrexate was a concern but thought to be unlikely after a single dose. Pulmonology was involved and agreed with single-dose management. Following a thorough discussion of the risks and benefits with the patient, an intramuscular dose of 84mg of methotrexate was administered on hospital day 13 as calculated by  $50 \text{ mg/m}^2$ .

Day 4 beta-hCG following methotrexate administration increased (by 57.5%) to 14 705 mIU/mL and imaging showed a gestational sac and yolk sac high within the fundus on the left outside of the endometrial cavity concerning an interstitial ectopic pregnancy (Figure 3). Day 7 beta-hCG was 14 643 mIU/mL and along with the gestational sac located in the uterine fundus, the transvaginal ultrasound now showed a crown-rump length of 0.39cm corresponding to a gestational age of 6 weeks and 1 day with a fetal heart rate of 91 bpm (Figure 4). The case was discussed with radiology, and an MRI was performed to obtain a more accurate location of the pregnancy prior to surgical management (Figure 5).

Imaging findings were discussed with the patient and she was taken to the operating room on hospital day 20 for an exploratory laparotomy. Multiple cystic lesions were noted to cover the entire uterus, and an area of enlargement was observed at the uterine fundus with surrounding vascularity (Figure 6). A wedge-shaped resection was performed to enucleate the area of swelling using electrocautery. The presumed pregnancy was removed intact and sent for pathology. Repair was performed in three layers including reapproximation of the endometrium in a continuous running fashion, and baseball stitches on the myometrium. There were no intraoperative or postoperative complications, and surgical pathology revealed uterine tissue consistent with ectopic pregnancy.

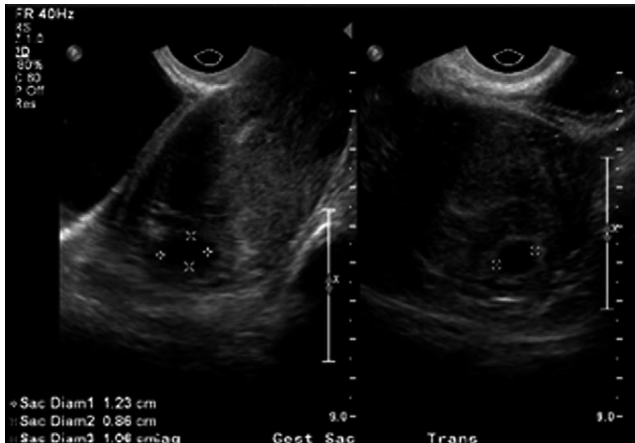
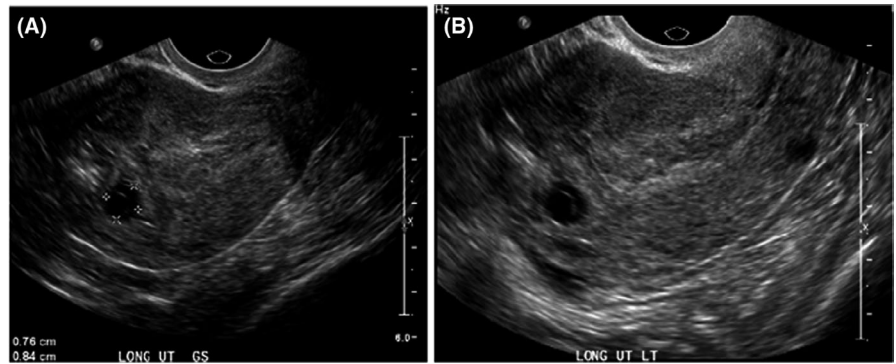
### 3 | INVESTIGATIONS

As per the American College of Obstetricians and Gynecologists, ultrasound findings of a hypoechoic area outside of the uterine cavity has a positive predictive value of



**FIGURE 1** Transvaginal ultrasound from hospital day 10 showing (A)  $1.64 \times 1.32$  cm hypoechoic structure in the fundal myometrium just left of the midline with (B) surrounding vascularity. Beta-hCG at the time was 5028

**FIGURE 2** Transvaginal ultrasound from hospital day 12 redemonstrating the fundal hypoechoic lesion. Beta-hCG at the time was 9335



**FIGURE 3** Transvaginal ultrasound from hospital day 16 - Day 4 following methotrexate administration: gestational sac and yolk sac high within the fundus on the left outside of the endometrial cavity concerning for an interstitial ectopic pregnancy. Beta-hCG at the time was 14 705

just 80%. In accordance with this, serial transvaginal ultrasounds for our patient were justified. However, a beta-hCG above the proposed “discriminatory level” of 3500 mIU/mL with no evidence of an intrauterine pregnancy results in findings of an ectopic pregnancy in 50%-70% of these cases. Our patient surpassed this level on just the second measurement of beta-hCG with a value of 5028 and had a simultaneous finding of a hypoechoic area in the fundal myometrium raising our suspicion for an interstitial versus cornual ectopic pregnancy.<sup>1</sup>

In previously reported cases, intramyometrial pregnancies are particularly difficult to diagnose with imaging and often will only be diagnosed once the patient is in the operating room.<sup>2</sup> However, MRI has been useful when distinguishing between unruptured and ruptured intramyometrial pregnancies.<sup>5</sup> According to Ko et al unruptured intramyometrial gestations appear as a homogenous hyperintense mass whereas ruptured gestations show a heterogenous signal intensity on T2-weighted images.<sup>5</sup> In our case, MRI was obtained in order to better define the location of the suspected ectopic pregnancy, but in retrospect have the homogenous hyperintense

mass on T2-weighted images as defined by Ko et al. This finding may have aided the correct diagnosis of an intramyometrial pregnancy preoperatively.

#### 4 | DIFFERENTIAL DIAGNOSIS

Intramyometrial ectopic pregnancies are difficult to diagnose in terms of both beta-hCG and imaging. These pregnancies typically rupture around 12 weeks of gestation as opposed to 6 weeks for a tubal pregnancy and on imaging may be misdiagnosed as interstitial/cornual ectopic, degenerating myoma, sarcoma, molar pregnancy, adenomyoma, or necrotic leiomyoma.<sup>6</sup> To complicate the diagnosis further, the uterine areas of perivascular epithelioid cell differentiation (PEComas) of tuberous sclerosis can distort the myometrium and are often misdiagnosed as leiomyomas, which were identified on our patient’s baseline transvaginal ultrasound earlier in the same year.<sup>6,7</sup> A possible leiomyoma continued to be a differential diagnosis on radiology reports for our patient up until the day of methotrexate administration when her beta-hCG was 9335 mIU/mL.

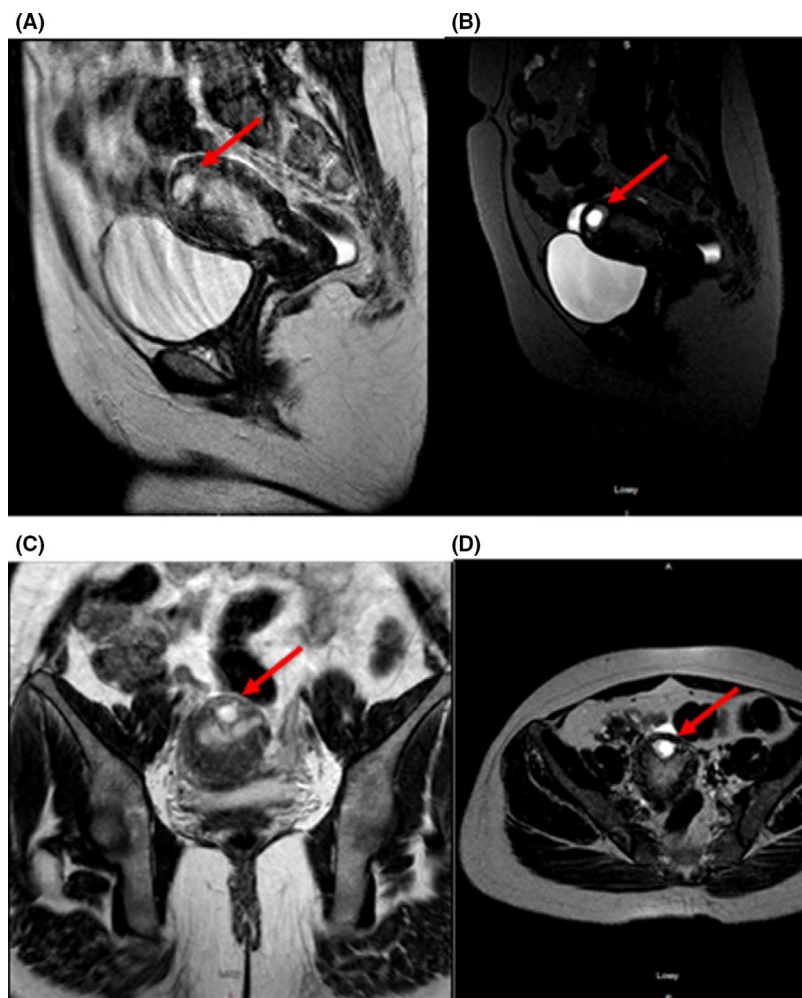
For the majority of her hospital stay, our patient was managed as a pregnancy of unknown location, as there lacked proper imaging demonstration of a gestational sac with a yolk sac or an embryo.<sup>1</sup> Although pregnancy of unknown location is considered a transient state rather than a proper diagnosis, it can help to avoid unnecessary exposure to methotrexate and rule out a possible early intrauterine pregnancy.<sup>1</sup> An ectopic pregnancy was only diagnosed when a gestational sac and yolk sac were found within the uterine fundus at a beta-hCG of 14 705 mIU/mL, and like many previously reported cases of intramyometrial pregnancies, our patient was only definitely diagnosed when in the operating room.<sup>2</sup>

#### 5 | TREATMENT

Different modalities of treatment can be utilized for all types of ectopic gestations and must take into consideration the size of the lesion, patient’s hemodynamic status, comorbidities of



**FIGURE 4** Transvaginal ultrasound from hospital day 19 - Day 7 following methotrexate administration: (A) gestational sac located in the uterine fundus (B) crown-rump length of 0.39 cm corresponding to a gestational age of 6 weeks and 1 day (C) fetal heart rate of 91 bpm. Beta-hCG at the time was 14 643



**FIGURE 5** MRI from hospital day 19 - Day 7 following methotrexate administration: T1 (A) and T2 (B) sagittal views with arrows demonstrating saclike structure in the fundal myometrium with minimal myometrium peripheral to the gestational sac. T1 (C) and T2 (D) axial views with arrows demonstrating the same. Beta-hCG at the time was 14 643

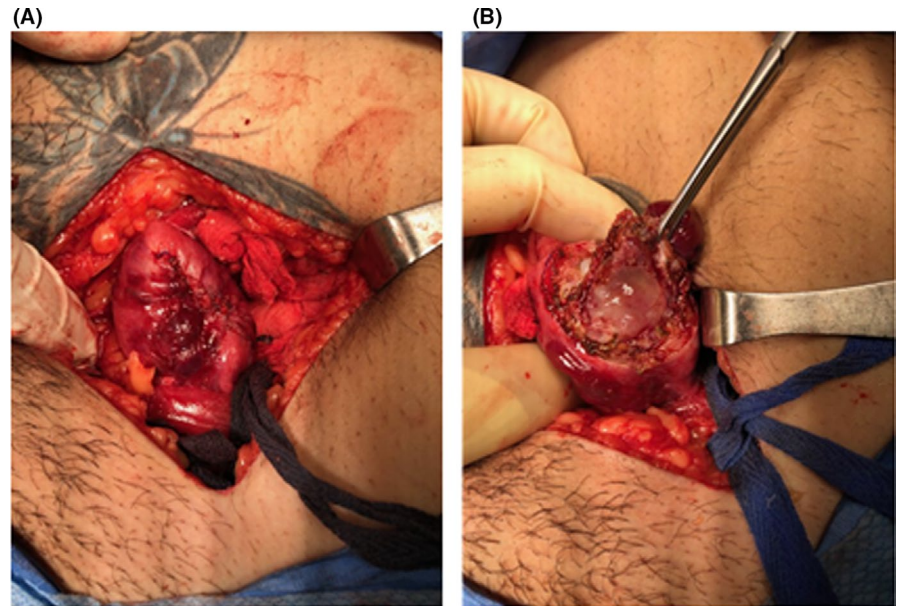
the patient, and also the desire for future fertility.<sup>8</sup> One treatment modality may be expectant management if it appears that the gestation is not progressing and observed beta-hcg values are decreasing appropriately. However, conservative management can still be achieved using systemic administration of methotrexate or ultrasound-guided methotrexate injection into the chorionic cavity of patients in a pregnancy without a fetal heartbeat (or in combination with fetal

injection of potassium chloride in cases of the presence of a fetal heartbeat).<sup>5</sup>

Nonradical surgical management of myometrial pregnancy by enucleation or wedge resection with myometrial reconstruction may be performed.<sup>4</sup> Additionally, conservative laparoscopic excision is possible without damage to myometrial integrity.<sup>5</sup> Other surgical treatment modalities include uterine artery embolization, excision by mini-laparotomy



**FIGURE 6** Intraoperative findings of (A) area of enlargement at the uterine fundus with surrounding vascularity, and (B) intact gestational sac enucleated from myometrium confirmed by pathology



which our patient underwent due to provider preference for complete removal of products of conception, hysterotomy, and/or hysterectomy when warranted due to uterine rupture with hemodynamic instability.<sup>4,9</sup>

## 6 | OUTCOME AND FOLLOW-UP

In our case, the beta-hCG dropped to 4486 mIU/mL by postoperative day 1. She was discharged from the gynecology service on postoperative day 5, and from the hospital on hospital day 25 after resolution of the pneumothorax. The patient was then followed up at our gynecology clinic until her beta-hCG dropped to nonpregnancy levels. She has since been seen at our clinic for routine annual gynecologic follow-up.

## 7 | DISCUSSION

Tuberous sclerosis is a tumor suppressor gene disorder caused by mutations in the genes TSC1 or TSC2 which lead to the development of benign tumors involving smooth muscle cells in multiple organs.<sup>10</sup> In this case report, our patient had a known history of tuberous sclerosis with prior imaging showing suspected hepatic and renal angiomyolipomas as well as pulmonary lymphangiomyomatosis. In the known literature, the uterus is one of the most common locations for these types of pathologies, including perivascular epithelioid cell differentiation (PEComas). These benign growths may infiltrate extensively into the myometrium causing consequent loss of myometrial contraction strength and, thus promote large hemorrhagic cavities which may disrupt into the endometrial cavity.<sup>11</sup> We speculate that these findings alone may have predisposed our patient to a myometrial pregnancy.

In accordance with the guidelines provided by the American College of Obstetricians and Gynecologists for ectopic pregnancies, it may have been prudent to administer methotrexate on just the second measurement of beta-hCG combined with the transvaginal ultrasound findings in any other patient.<sup>1</sup> However, our case was complicated by a known history of pulmonary lesions and current admission for persistent pneumothorax. Active pulmonary disease is an absolute contraindication for methotrexate administration, and the persistent pneumothorax requiring chest tube suction made the patient a nonideal candidate for surgical management. Furthermore, this was a highly desired pregnancy. For these reasons, methotrexate was administered at a beta-hCG of 9335 mIU/mL. Studies have shown that methotrexate for ectopic pregnancy has a failure rate of at least 14.3% when given to patients with beta-hCG higher than 5000 mIU/mL. She was at further risk of failure of methotrexate due to the 95% increase in her initial two values of beta-hCG. Our patient was found to have failed medical management with methotrexate after beta-hcg values continued to rise. For this reason, the decision was made to proceed with surgical management. Further imaging using MRI suggested an interstitial vs cornual pregnancy and intraoperative findings were consistent with a myometrial pregnancy.

In the review of literature, there is only one known case of intramyometrial ectopic pregnancy in the setting of Tuberous Sclerosis. Glass et al reports a patient with tuberous sclerosis in which an intramyometrial pregnancy ruptured at 7 weeks gestation.<sup>12</sup> Their diagnosis was confirmed after pathology from a suction curettage did not reveal chorionic villi. Surgical management via diagnostic laparoscopy converted to exploratory laparotomy was performed secondary to findings of ectopic pregnancy rupture. In retrospect, had an intramyometrial pregnancy been suspected

in our case, the risk of 2.5% maternal mortality due to uterine rupture would have greatly outweighed the benefit of a highly desired intrauterine pregnancy, and surgical management may have been the first step in management as opposed to methotrexate.

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### CONFLICTS OF INTEREST

There are no conflicts of interest to disclose for this manuscript.

### AUTHOR CONTRIBUTIONS

Dr. Neha Sharma, Dr. Michele Agustin, and Dr. Ariel Polonsky contributed equally to the acquisition of case details and background literature. They were also equal contributors to the drafting and editing of the manuscript for final approval under the guidance of Dr. Lance Bruck.

### ETHICAL APPROVAL

This manuscript does not contain personal and/or medical information about an identifiable living individual.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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