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REVIEW

Intramural ectopic pregnancy following pelvic adhesion: case report and literature review

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Abstract

Background Intramural pregnancy is an uncommon type of ectopic pregnancy, where the gestational sac is completely encircled by myometrium and unconnected with endometrial cavity, fallopian tubes or round ligament. Owing to its potentially life-threatening hemorrhage and uterine rupture, early diagnosis and management are urgently required. We present a case of a woman undergoing zigzag medical procedures, which featured non-consensus preoperative diagnosis of intramural and interstitial pregnancy and an intramural ectopic pregnancy ultimately confirmed and successfully removed by emergency laparoscopy. Additionally, we present a review of the related literature and discuss its varied clinical features, imageological characters, diagnosis, differential diagnosis and multiple treatments.

Methods A comprehensive bibliographic search through PubMed, using keywords: intramural ectopic pregnancy. Relevant literatures published from January 2013 to April 2019 were reviewed.

Results Twenty-four cases in total for intramural ectopic pregnancy including this report were reviewed. Diagnoses were mainly made by ultrasound images. Most patients had a history of uterine surgery or intrauterine operation and had been surgically resected. None of the mothers were in danger, but only one case had live birth at 37 weeks of gestation.

Conclusion Non-specific clinical presentation and non-uniform ultrasound criteria pose a challenge for us to make timely and accurate management. Integrated radiological examinations and communication and cooperation between sonographers and gynecologists play a vital role in diagnostic accuracy and selecting the optimal therapeutic method of an intramural pregnancy.

Keywords Intramural pregnancy · Transvaginal ultrasound · Transabdominal ultrasound · Power Doppler sonography · Management

Introduction

Intramural ectopic pregnancy refers to a gestational sac surrounded by the uterine wall without connection to the endometrial cavity and fallopian tubes or round ligament [1, 2]. Intramural pregnancy is extremely rare with an incidence rate of less than 1% of total ectopic pregnancies [3]. Several theories regarding intramural pregnancies have been proposed. These include implantation in the focus of adenomyosis or in the microscopic sinus tract formed during uterine trauma (previous myomectomy, dilatation and curettage and cesarean section) or serosal implantation of the conceptus following embryo transfer and in vitro fertilization (ET-IVF) or perimetrium inflammation, flawed decidualization or increased trophoblastic activity [4–8].

Women with intramural pregnancy often have an amenorrhea history and increased serum β-human chorionic gonadotropin (HCG) levels. Abdominal pain and vaginal bleeding are also some of the symptoms. However, aforementioned clinical symptoms are very similar to common obstetrical and gynecological issues, including early pregnancy, other types of ectopic pregnancy or gestational trophoblastic disease [3]. This makes early accurate diagnosis difficult.

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Ultrasound and magnetic resonance imaging (MRI) are common auxiliary techniques that have been used for diagnosis. Transvaginal ultrasound (TVS) is the preferred screening method due to it being noninvasive, convenient and inexpensive and offers real-time visualization. Intramural pregnancies are rare, and hence there is a lack of consensus regarding treatment guidelines for gynecologists.

We hereby report a patient with intramural ectopic pregnancy with the purpose to highlight variable symptoms and clinical course, diagnostic dilemma and multiple management of intramural pregnancy. In addition, we have summarized in this report all available published patient cases from January 2013 to April 2019.

Case Report

A 30-year-old patient, G1P1, was transferred to our institution for suspected intramural pregnancy. She had a history of amenorrhea for 70 days, unprovoked vaginal bleeding, and irregular menstrual cycles without dysmenorrhea. She initially visited the gynecology unit of a local hospital for induced abortion. Local TVS scans revealed a gestational sac (GS) measuring 9 × 8 mm located in the posterior uterine wall. In addition, a boundary between the gestational sac and endometrium was observed. Echogenic yolk sac and an embryo bud with primordial cardiac pulsation were observed within the gestation sac. Her β-HCG levels were 8155 mIU/ml. Four years previously, she underwent a low cesarean section. Gynecological examinations showed a slightly enlarged uterus, similar in size observed at 6 weeks of gestation. Transvaginal ultrasonogram indicated an echogenic structure measuring 10 × 7 × 8 mm in size at the posterior myometrium near the uterine fundus. Vitelline sac and heartbeat were observed inside. The endometrial cavity was not connected to the structure (Fig. 1a). Intra-myometrial arcuate vasculature was observed using color Doppler ultrasound (Fig. 1b). For comprehensive diagnosis, TAS was also performed. Two-dimensional sagittal ultrasonogram showed that the serosal surface of the heterogeneous echo mass had feeble myometrial tissue (Fig. 2a). Power Doppler sonography displayed trophoblastic peripheral blood flow (Fig. 2b). The patients' β-HCG level was 22,805 mIU/ml. Due to intramural pregnancies being rare, pre-surgical TVS revaluation was performed for confirmation. However, the last scan produced uncertainty with regard to an ectopic tubal pregnancy with potential risk of life-threatening bleeding (Table 2). Given the very high mortality rates of interstitial pregnancy, emergency laparoscopic exploration (salpingectomy on the affected side) was performed. During the procedure, a bulging mass measuring 4 × 3 × 3 cm was observed in the posterior wall below the left horn of the uterus with a purplish-blue-colored surface (Fig. 3). We observed that the posterior serosa layer was adhered to the surrounding intestine with bilateral adnexa of the uterus being normal. After injecting diluted terlipressin into the myometrium around the mass, a fusiform incision was made using a coagulation hook, which resulted in chorionic villous tissues bulging out. The product of conception was removed and the specimen was placed in a bag and completely removed from the ancillary port. The cavity left was explored carefully, and we found it blocked to the uterine cavity and fallopian tube. The defect in the myometrium was injected diluted methotrexate (MTX50 mg + NS10 ml) to kill the activity of possibly

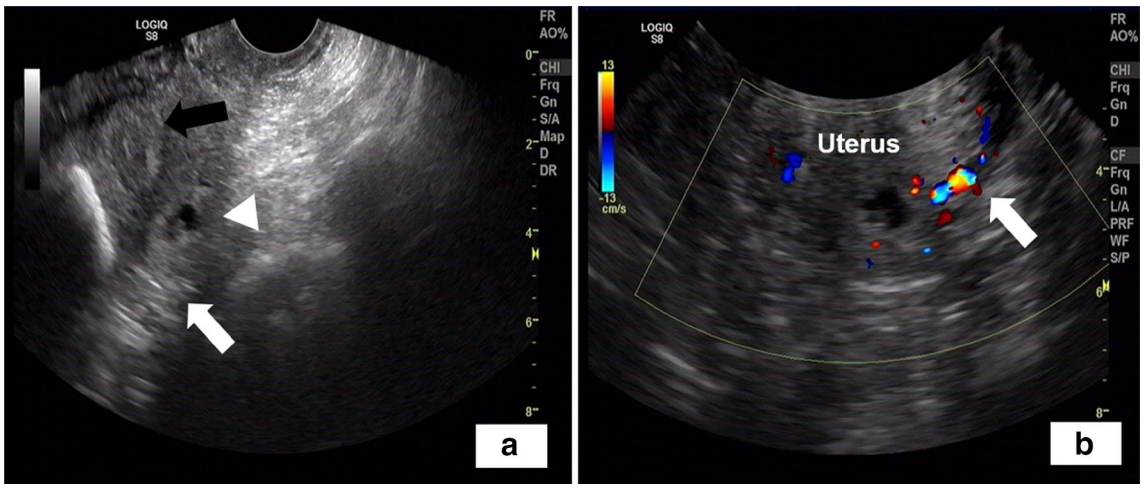

Fig. 1 **(a)** Transvaginal ultrasonogram indicated an echogenic structure (white triangle) at the posterior myometrium near the uterine fundus. The endometrial complex (black arrow) was not connected to the structure. The relationship between posterior wall and mass displayed unclearly (white arrow). **(b)** Color Doppler ultrasound showed the intra-myometrial arcuate vasculature (white arrow)

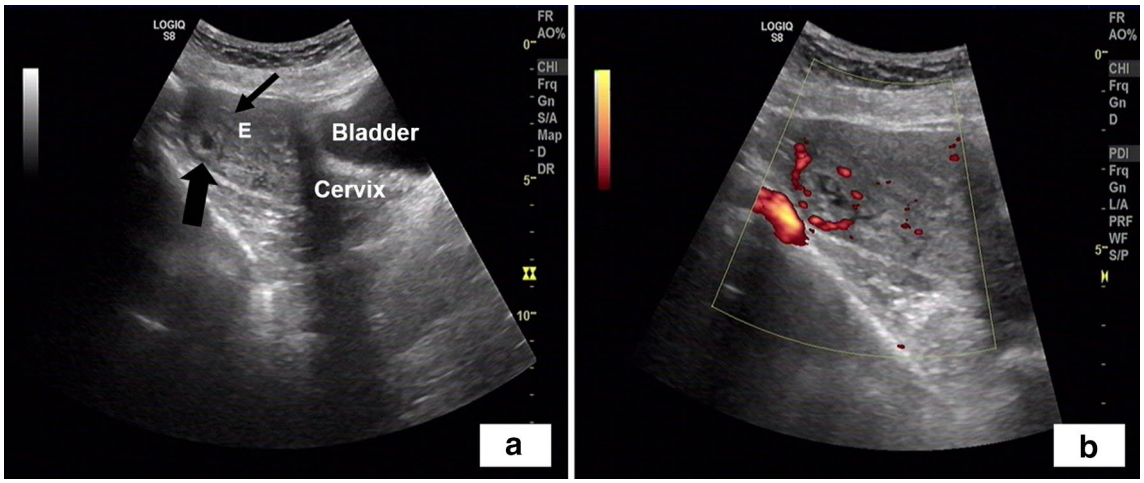

Fig. 2 **(a)** Two-dimensional sagittal ultrasonogram showed that the serosal surface of the heterogeneous echo mass had feeble myometrial tissue (coarse arrow). The endometrial–myometrial junction was displayed (thin arrow). **(b)** Power Doppler ultrasound displayed trophoblastic peripheral blood flow

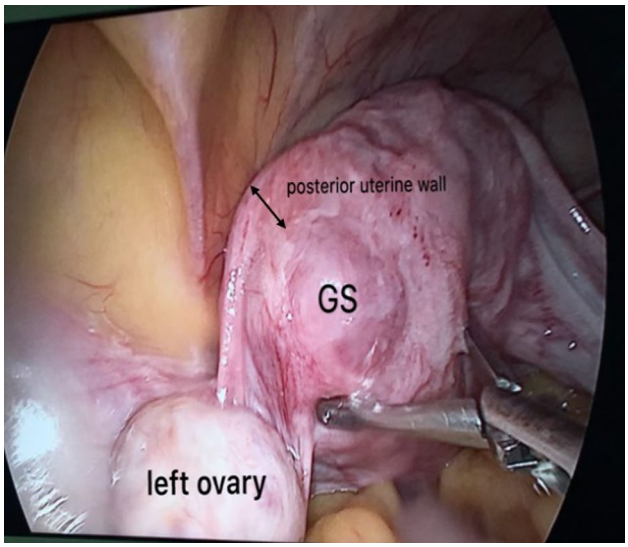

Fig. 3 Laparoscopic findings showed that a bulging mass was in the posterior wall below the left horn of the uterus (the distance has been marked as the black double arrow). The mass had a soft texture and purplish-blue-colored surface

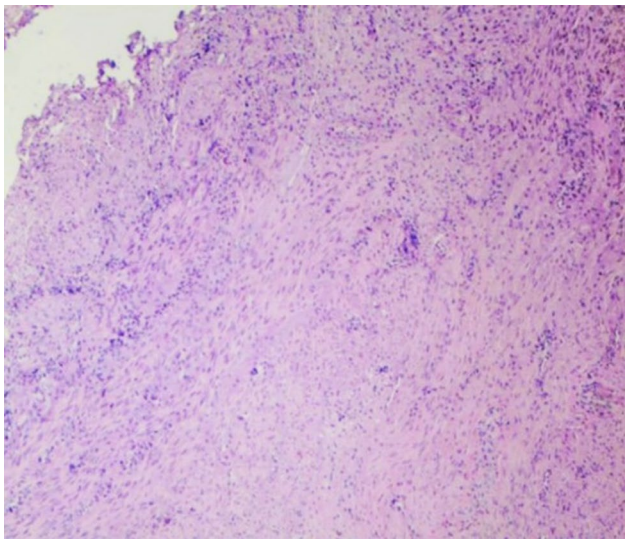

Fig. 4 Histopathological observation showed the characteristic chorionic villi and the smooth muscle tissue was infiltrated with trophoblast cells

residual trophoblast cells and then sutured intermittently (1-0 monocryl), while the wound was sutured continuously. Microscopically, the mass had characteristic chorionic villi and the smooth muscle tissue was infiltrated with trophoblast cells (Fig. 4). The patient's serum β-HCG level was 5000 mIU/ml on post-surgery day and declined to 2012 mIU/ml on the second day after surgery. The patient was well at discharge and had an uneventful follow-up course.

Methods

A comprehensive bibliographic search of PubMed was performed using the following MeSH terms: [intramural[All Fields] AND ("pregnancy, ectopic"[MeSH Terms] OR ("pregnancy"[All Fields] AND "ectopic"[All Fields]) OR "ectopic pregnancy"[All Fields] OR ("ectopic"[All Fields] AND "pregnancy"[All Fields]))]. The search was limited to articles published from January 2013 to April 2019 (Fig. 5). All citations identified were selected for abstract

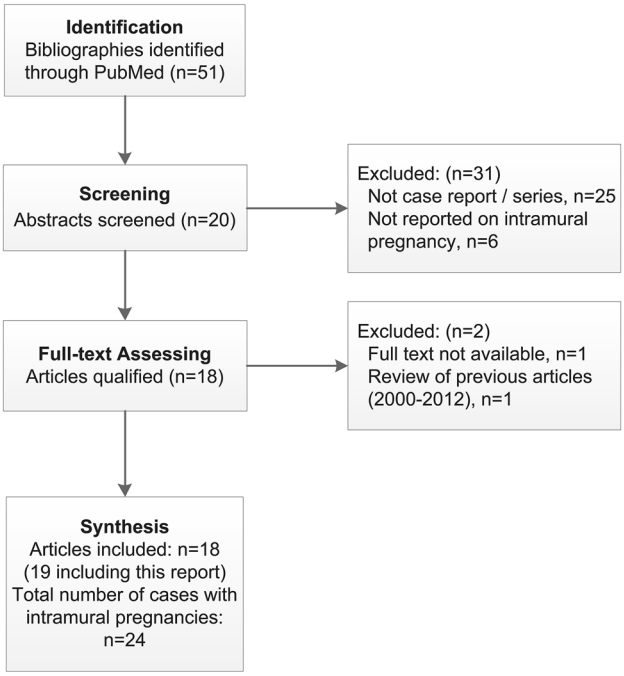

Fig. 5 Flowchart of the literature searching on April 2019

review. Abstracts that did not relate to case report/series or those with themes not related to intramural pregnancy were excluded. The remaining publications were selected for full-text evaluation and those considered relevant were included for final review. After the first cycle of review, cross-reference searches were performed until all relevant publications were reviewed. Afterward, relevant data were extracted from case descriptions, which included, gestational age, GPLA status and clinical/patient characteristics including amenorrhea history, vaginal bleeding and abdominal pain and other symptoms such as vomiting and nausea. Diagnostic data included gynecology and obstetrics surgical history, TVS or TAS images (especially for GS location), pelvic MRI and serum HCG levels. Additionally, pre-surgical or pretreatment diagnosis, the type of therapeutic intervention and maternal and fetal outcomes were collected [9–26] (Table 1).

Results

The flowchart results from our search are shown in Fig. 5. Fifty-one relevant citations from January 2013 to April 2019 were retrieved from PubMed. All abstracts were evaluated, and 20 were selected for full-text review. Thirty-one records were excluded after abstract review, i.e., 25 were not case/case series and six were not based on intramural pregnancy. From the 20 publications selected for full-text evaluation, two were excluded, i.e., one lacked full-text availability, and the other was a review of previous related publications (2000–2012). Nineteen articles (24 cases) in total related to intramural pregnancy including our case report in this publication met our criteria and were reviewed (Table 2). Bernstein et al. [2] performed a review of 25 articles published from 1957 to 2000. During that time, the majority of reported intramural pregnancies were usually diagnosed after uterine rupture (necessitating hysterectomy) and confirmed by post-surgical pathology. However, clinicians and experts believed that ultrasound provides reliable pre-surgical detection rates, with available conservative management including methotrexate or focal excision. About 22 cases of intramural pregnancy from 2000 to 2012 were reviewed by Kirk et al. [27]. In their study, morbidity and clinical or imaging characteristics together with management were comprehensively analyzed. They proposed that the lack of knowledge regarding the disease and its rarity were possible reasons why diagnosis could not be made using ultrasound. Apart from conventional ultrasound, three-dimensional ultrasound and MRI could be useful for making a proper diagnosis. Moreover, treatment could be diverse instead of only surgical.

In our review, maternal gestation ranged from 4 + 3 weeks to 37 weeks. Except for two fetal cases, 68.2% (15/22) were in the first trimester. The two most common symptoms were vaginal bleeding/discharge (54.2%) and abdominal/pelvic pain (33.3%). Three quarters of patients had a positive β-HCG reading, while the remaining cases lacked this information. Except for three primigravid women, the rest of the patients had gynecological and obstetrics history: suction curettage (50.0%) (including misdiagnosis of intrauterine pregnancy), cesarean section (8.3%), laparoscopic surgery for endometriosis (8.3%), normal vaginal delivery (8.3%), open/laparoscopic myomectomy (12.5%) and ET-IVF (4.2%). All cases underwent ultrasound examinations. Over a third of the studies performed additional MRIs (37.5%), and one study performed computed tomography examination (CT). Two cases were examined using three-dimensional ultrasound. The most frequent GS location was in the posterior uterine wall (70.8%) and mostly in the left fundus. For two cases, GS was located above the level of the internal os with hysterectomy due to uncontrolled bleeding. The remaining cases were located in the front uterine wall and one located in the anterior myometrium of the lower uterine segment. The majority of cases (62.5%) were suspected or diagnosed using TVS/MRI images prior to treatment. Six cases were initially misdiagnosed as missed abortion/intrauterine pregnancy and underwent unnecessary suction curettages. Cornual pregnancy/invasive molar pregnancy in two studies were not excluded. One case was misdiagnosed with leiomyoma and adenomyosis, and the other was misdiagnosed as an intrauterine pregnancy because the fetus at 37 weeks of gestational age was difficult to locate. About

Table 1 Details of intramural pregnancies identified in January 2013–April 2019

Authors	Years	Gestational age	Manifestations	Ultrasound features	Preoperative or pretreatment diagnosis	History of gynecology and obstetrics	Management
Qi et al. (index case)	2019	6 weeks	Unprovoked vaginal bleeding and amenorrhea history, HCG level was 22,805 mIU/ml	An echogenic structure measuring 10×7×8 mm in the posterior myometrium near the uterine fundus with vitelline sac and heartbeat	Suspected intramural pregnancy and not excluded interstitial pregnancy	G1P1, a cesarean section	Laparoscopy and resection
Ishiguro et al. [9]	2018	8 weeks	Severe abdominal pain, HCG was 2276mIU/ml	An gestational sac (16 mm in diameter with an embryo that was 10 mm in length) located at the subserosal site of the myomectomy scar	–	Primigravid woman, two laparoscopic myomectomy, ET-IVF	Emergency laparotomy and evacuation
Vagg et al. [10]	2018	12 weeks	Vaginal discharge and pain in the right iliac fossa and a positive β-HCG	TVS and MRI revealed a gestational sac (8.0×7.9×7.0 cm) within the myometrium of the right uterine cornua, overlying a thin 3-mm layer of myometrium, placental invasion to the previous myomectomy site	Intramural pregnancy	Two normal vaginal deliveries and an open myomectomy	Abdominal hysterectomy and bilateral salpingectomy
Mahmoud et al. [11]	2017	4^{+3} weeks	Amenorrhea history and minimal vaginal bleeding, lower abdominal pain, nausea and vomiting, β-HCG level was 7928 mIU/ml	An empty uterine cavity and a 28-mm, well-defined gestational sac located in the anterior myometrium of the lower uterine segment, an embryo with positive cardiac activity, a yolk sac and a crown-rump length (CRL) of 1.1 mm	A cesarean scar ectopic pregnancy	G8P7, a cesarean section	Exploratory laparotomy and evacuation
Shan et al. [12]	2017	5^{+5} weeks	Amenorrhea history and β-HCG level was 14,153 mIU/ml	A mixed echogenic mass measuring 5.1×4.6 cm located within the posterior wall of the uterine fundus with an abundant blood supply and separated from the uterine cavity. MRI demonstrated an intramural mass	Diagnosed preliminarily choriocarcinoma and not excluded intramural pregnancy	G2P1	A hysteroscopy and laparoscopic removal due to side effects and no obvious therapeutic effects of chemotherapy

Table 1 (continued)

Authors	Years	Gestational age	Manifestations	Ultrasound features	Preoperative or pretreatment diagnosis	History of gynecology and obstetrics	Management
Kong et al. [13]	2017	17^{+2} weeks	–	A gestational sac within the myometrium not connected with the cavity. Fetus with heartbeat and placenta previa. MRI showed a fetus with clear organs compressed the lower uterine segment and embedded into the myometrium	–	G1P0, 1 uterine curettage procedure	Abdominal hysteroplasty and excision under temporary balloon occlusion of abdominal aorta
Nana et al. [14]	2017	Case1 = 8 weeks	Amenorrhea history and nausea, β-HCG level was 15,000 mIU/ml	A heterogeneous mass measuring 3.7 cm × 3.3 cm in the posterior wall, extending to the uterine serous layer, MRI indicated an irregular signal area in the left wall within the myometrium of the uterus	Suspected intramural pregnancy	G2P1, laparoscopic surgery for endometriosis and one curettage procedure for the missed diagnosis of intrauterine pregnancy	Hysteroscopy showed an empty uterine cavity and laparoscopic removal
		Case2 –	Irregular vaginal bleeding and vomiting, β-HCG level was 10,011.57 mIU/ml	A heterogeneous mass measuring 4.2 cm × 2.9 cm in the left posterior wall of the uterus	Suspected intramural pregnancy	G1P0, 1 curettage procedure	Laparoscopic resection
		Case3 = 8^{+4} weeks	Amenorrhea history and severe abdominal pain, β-HCG level was 32,100.33 mIU/ml	A heterogeneous echogenic mass (5.4 cm × 4.4 cm) in the right side of the uterine wall, close to the corneal tissue and an embryo bud (with heartbeat) not connected with the endometria	Suspected intramural pregnancy	G4P0	Hysteroscopy showed an empty uterine cavity and laparoscopic removal
Chida et al. [15]	2016	7 weeks	–	TVS showed a gestational sac with a live fetus located within fundic uterine wall, MRI showed the sac implanted into the myometrial defect	Intramural pregnancy	G1P0, one dilation and curettage	Laparotomy and resection after uterine artery embolization

Table 1 (continued)

Authors	Years	Gestational age	Manifestations	Ultrasound features	Preoperative or pretreatment diagnosis	History of gynecology and obstetrics	Management
Li et al. [16]	2016	18.5 weeks	Asymptomatic	Ultrasound and MRI showed an empty endometrial cavity and a gestational sac with a fetus implanted in the right posterior lateral side of the uterus fundus	Intramural pregnancy	G1P0, one curettage procedure at 9 weeks of gestation for termination of pregnancy. The gestation continued until the patient felt the fetal movement	Laparotomy under temporary balloon occlusion of abdominal aorta
Wang et al. [17]	2015	8 weeks	Persistent vaginal bleeding and β-HCG level was 1069 mIU/ml	An ill-defined fundal mass (30 × 25 mm) near the left fundus	Suspected an embryonic left cornual pregnancy or an invasive molar pregnancy	G3P1A1 First suction curettage for misdiagnosed missed abortion, second for intrauterine residues (not obtained biopsy specimen)	Hysteroscopy revealed an empty uterine cavity and visible bilateral ostia, laparoscopy and excision
Liu et al. [18]	2014	–	Intermittent vaginal bleeding, intra-operative β-HCG was 106.50 IU/l and then decreased to 16.55 IU/l after surgery	Color Doppler ultrasound revealed uneven echoes in the muscle layers and sufficient blood flow signals in an enlarged area of the uterus	Leiomyoma and adenomyosis	G1P1, 24 years of primary dysmenorrhea and 5 years of uterine leiomyoma	Laparoscopic subtotal hysterectomy
Bannon et al. [19]	2013	10 weeks	β-HCG decreased from 11,843 to 2490 mU/ml	Three-dimensional TVS and CT revealed the gestational sac located in the posterior left lateral wall of the uterus entirely surrounded by myometrium	Diagnosed initially missed abortion, finally diagnosed intramural pregnancy (based on ultrasound and CT)	G1P0, an open myomectomy for a large, Left-sided, posterior leiomyoma. One suction curettage for missed abortion	A single dose of systemic MTX and laparoscopic removal
Sharma et al. [20]	2013	12 week	Amenorrhea history and active heavy bleeding, β-HCG level was 28,700 mIU/ml	A heterogeneous space occupying lesion (61 mm × 60 mm) in the cervical region with empty endometrial canal and closed internal os	Cervical ectopic pregnancy	–	Emergency laparotomy and hysterectomy
Wang et al. [21]	2013	6 weeks	Lower abdominal pain and amenorrhea history, β-HCG level was 12,250 mIU/ml	TAS and MRI revealed a gestational sac with a yolk sac was surrounded by myometrium (located at the midline of the fundus uterus) and distinct from the endometrial cavity	Suggested intramural pregnancy	G2P0A1, 1 suction curettage	Uterine artery embolization

Table 1 (continued)

Authors	Years	Gestational age	Manifestations	Ultrasound features	Preoperative or pretreatment diagnosis	History of gynecology and obstetrics	Management
Petit et al. [22]	2013	37 weeks	Asymptomatic	TVS confirmed anterior placenta previa without placenta accreta	Intrauterine pregnancy	–	Cesarean section (yielding a healthy girl) and hysterectomy for uncontrol uterine bleeding
Ye et al. [23]	2013	8^{+1} weeks	Lower abdominal pain and amenorrhea history and β-HCG level was 15,000 mIU/ml	A heterogeneous echogenic area (3.7 cm × 3.3 cm) stretching to the serosa layer in the posterior uterine wall, MRI showed an irregular-shaped signal within the myometrium in the left wall of the uterus	Suspected intramural pregnancy	G2P1, a laparoscopic surgery for endometriosis	Hysteroscopy revealed an empty uterine cavity and laparoscopic unilateral uterine arterial occlusion and removal
Memtsa et al. [24]	2013	Case1 = 8 weeks	Heavy vaginal bleeding, β-HCG level was 1693 IU/l	Retained products of conception located within the myometrium of the left posterior uterine wall, with no communication with the endometrial cavity	Partial intramural pregnancy	G5P3 three spontaneous vaginal deliveries at term. Previous curettage for an incomplete miscarriage	Conservative management
		Case2 –	Heavy vaginal bleeding	Retained products measuring 1.5 cm in mean diameter with pregnancy tissue partially embedded in the myometrium of the posterior uterine wall	Retained products of conception	G1P1 A cesarean section at 41 weeks' gestation, 1 dilatation and curettage (but remained symptomatic)	Evacuation and removal under ultrasound guidance
		Case3 = 6 weeks	Vaginal bleeding and pain, β-HCG increased from 398 to 1159 IU/l	A highly vascular 8 mm focus of hyperechoic tissue deep in the posterior wall of the uterus	Diagnosed tentatively intramural pregnancy	Primigravid woman	Ultrasound-guided biopsy and intra-fetal injection of MTX (25 mg)
		Case4 = 11 weeks	Heavy vaginal bleeding at 20 weeks' gestation	A gestational sac containing a live 11-week fetus was seen deep in the myometrium of the left uterine wall just above the level of the internal os	Suspected cervical pregnancy	Primigravid woman	Continue the pregnancy and an emergency hysterectomy due to uncontrolled bleeding

Table 1 (continued)

Authors	Years	Gestational age	Manifestations	Ultrasound features	Preoperative or pretreatment diagnosis	History of gynecology and obstetrics	Management
Wu et al. [25]	2013	8 weeks	Amenorrhea history and dull lower abdominal pain and β-HCG level was 87,474 mIU/ml	An ill-defined fundal mass of 3.8×2.7 cm without a definitive fetal pole, located adjacent to the right cornua, high blood flow at the periphery of the mass	Suspected an anembryonic right cornual pregnancy or an invasive molar pregnancy	G3P0, 2 curettages in the trimester (but undetected pregnancy product)	Hysteroscopy and laparoscopic removal and an intramuscular injection of MTX (25 mg)
Wang et al. [26]	2013	7^{+1} weeks	Intermittent vaginal bleeding and β-HCG level was 36268 IU/l	Three-dimensional sonography showed the gestational sac was located in the left posterior side of the myometrium, about 1.4 cm above the internal os, with a sinus tract connecting the sac and endometrial cavity, MRI indicated a trabecular pattern of heterogeneous signal intensity in the mass and enhanced tree-like solid components	Intramural pregnancy	G2P0, a dilation and curettage	Hysteroscopic local excision and systematic injection of MTX

Table 2 Details of three transvaginal ultrasound reports and HCG levels

Time	Ultrasound reports	HCG levels (mIU/ml)
2019.02.09	–	8155
2019.02.13 (local hospital)	A gestational sac measuring 9×8 mm located in the posterior uterine wall. In addition, a boundary between the gestational sac and endometrium was observed. Echogenic yolk sac and an embryo bud with primordial cardiac pulsation were observed within the gestation sac.	
2019.02.13 (first scan in our hospital)	Transvaginal ultrasonogram indicated an echogenic structure measuring 10×7 × 8 mm in size at the posterior myometrium near the uterine fundus. Vitelline sac and heartbeat were observed inside. The endometrial cavity was not connected to the structure.	22,805
2019.02.14 (second scan in our hospital)	A mixed echogenic mass measuring 2.6×2.0 cm located in the left horn of uterus, which contained a gestational sac about 12.2×8.3 mm in size. Echogenic yolk sac and an embryo bud with primordial cardiac pulsation were observed. There was no intraabdominal bleeding.	–
2019.02.15 (post-surgery day)	–	5000
2019.02.16 (the second day after surgery)	–	2012

half of the cases (41.7%) had laparoscopic excision/hysterectomy and five patients underwent hysterectomy. Only one underwent conservative management and one was treated by injecting MTX under ultrasound guidance. Three unilateral/bilateral uterine artery embolizations were performed with excellent outcomes. Two cases with mid-trimester gestation were treated using temporary balloon occlusion of the abdominal aorta. One case had ultrasound-guided excision and one case had hysteroscopic local excision combined with MTX. None of the mothers had life-threatening conditions. One case had a live birth at 37 weeks of gestation.

Discussion

Intramural pregnancy is viewed as a rare ectopic pregnancy and refers to extrauterine conception that is separate from the endometrial cavity and tubes or round ligament. Based on reported cases, we retrospectively summarize that intramural pregnancies may present a variety of symptoms and clinical courses and are influenced by the location of the conception, extent of myometrium implantation and gestational size. However, due to specific anatomical locations, intramural pregnancies are too hard to diagnose until uterine rupture [3, 7]. Larry McGowan, MD proposed that the ever-growing conceptus confined to the myometrium may result in a pressing rupture. This may be due to the pulling force of the unusual myometrial vasculature or the thinner myometrium overlying it [28]. Symptoms and physical signs of hemoperitoneum and hypovolemic shock inevitably leads to an urgent need for hysterectomy. Advances made in diagnostic ultrasonography have allowed for earlier diagnosis. In addition, appropriate conservative management could be offered to preserve fertility. This may help decrease the rate of resultant uterine rupture and associated morbidity and mortality.

Intramural pregnancies can have varied etiologies. They may mirror prior uterine traumas, including myomectomy, perforation, dilation and curettage and cesarean section [4, 5, 19]. Microscopic sinus tracts formation is beneficial to the conceptus entering into the myometrium. In addition, penetration into the uterine wall by the conceptus is associated with increased trophoblastic activity and is associated with flawed decidualization. Perimetrium inflammation is more likely relevant with uterine serosa implantation of a fertilized ovum [1, 3, 6]. Intramural pregnancy may also occur within the focal endometrial implantation of endometriosis and during ET-IVF [3, 7, 8, 18]. In our patient, the only recognizable risk factor was pelvic adhesions caused by the history of cesarean section.

With the development of high gray-scale resolution TVS, and with the aid of rapid detection of serum β-HCG using immunoassays, early detection and localization is possible. One exception is pregnancy with leiomyomata, which can obscure the gestational sac [18]. Interestingly, the most reported location was in the posterior uterine wall where adenomyosis is also more commonly located. This seems to be a more reasonable explanation why pregnancies with adenomyosis locate to the posterior wall, although only two cases were observed [12, 22]. In the past, diagnosis was made at a more advanced gestational age (approximately 11–30 weeks' gestational age) [19]. However, the majority of maternal gestations in this review were diagnosed in the first trimester (less than 12 weeks). Kurt et al. indicated that initial ultrasonography could diagnose ectopic pregnancies with high specificity (99.9%) and had positive predictive value (98%) in symptomatic first-trimester pregnancies [29]. In a prospective

study, George et al. demonstrated that 90.9% of ectopic pregnancies could be visualized using pre-surgical TVS [30]. Indeed, ultrasonic characteristics are the basis for successful diagnosing of intramural pregnancies. This is because the gestation sac (or mass) is completely surrounded by the myometrium and separate from the endometrial cavity and fallopian tube. In addition, an embryonic and primitive heartbeat could sometimes be observed [14]. Ultrasound images should allow for a clear visualization of the endometrial–myometrial junction in order to delineate the endometrial cavity and detect extensions of trophoblasts into the myometrium. In addition, three-dimensional (3D) ultrasound could provide clear images of the endometrial–myometrial junction, which is often affected by adenomyosis, and thus could be very helpful for the detection of pregnancy with adenomyosis [31].

In clinical practice, a diagnosis of intramural pregnancy is mainly based on the pathological finding of villi in the myometrium and HCG levels [18]. When initial ultrasound diagnosis of ectopic pregnancy is made without evidence of a yolk sac or embryo, or when HCG levels are low, or when the patient has significant bleeding, misdiagnoses could occur [29]. A total of seven cases which we reviewed were initially misdiagnosed as missed abortion/intrauterine pregnancy, of which, six cases underwent unnecessary suction curettages and one patient delivering a baby. Misdiagnosis was mainly due to incorrect localization of the gestational sac, and was likely due to operator inexperience and indistinguishable imaging features. Previous studies have shown that early unruptured intramural pregnancy could simulate a degenerating myoma or a pregnancy coupled with sacculation, diverticulum or congenital uterine malformation [28].

Previous studies have demonstrated that the specificity and sensitivity of transabdominal scanning were lower compared to TVS [32]. However, only a quarter of the publications we reviewed used TAS images for the diagnosis of intramural pregnancy. Our patient was diagnosed using TAS to confirm the location of the mass. Transabdominal sagittal images showed that the myometrium overlying the mass was very thin, which was confirmed intra-surgically. In addition, we used power Doppler imaging (PDI) to clearly display the trophoblastic peripheral blood flow, which was characterized by slow blood flow. In contrast to color Doppler flow imaging (CDFI), some publications have reported that PDI is more sensitive and continuous, especially for vessels with 3–8 mm in diameter. Another advantage is that PDI is unaffected by velocity, direction and detection angle. In our review, three-dimensional PDI was performed in one case to observe blood flow. One possible reason is that blood flow signals can be distinctly displayed using CDFI.

Ovarian corpus luteum cysts may provide meaningful insights to determine ectopic pregnancies using TVS, with 70–85% of cases having them on the ipsilateral side [33]. However, none of our reviewed cases (including the case in this report) had a corpus luteum cyst.

When intramural pregnancies are encountered, clinicians usually request for a second scan, as these types of pregnancies are rarely observed [27]. When the second ultrasound diagnosis indicates an interstitial pregnancy, which can easily lead to massive bleeding and high maternal mortality rates [34], gynecologists will perform emergency surgery. There is a difficulty in differentiating intramural and interstitial ectopic pregnancies. Sonographic criterion for interstitial pregnancy is that a very thin myometrial layer surrounding the extrauterine sac and the discovery of "interstitial line sign" which is an echogenic line connecting the margin of the intrauterine gestational sac with the superolateral aspect of the endometrium [35, 36]. Clinicians often use the term cornual ectopic pregnancy interchangeably with interstitial pregnancy. However, cornual pregnancy refers more specifically to intrauterine implantation of the embryo in one horn of a bicornuate uterus, a rudimentary horn of a unicornuate uterus, or the lateral half of a septate uterus [37]. In our review, two cornual pregnancies-ruled-out cases underwent hysteroscopy, which revealed visible bilateral ostia [17, 25].

Another disease that needs to be differentially diagnosed is gestational trophoblastic neoplasm, which shows abnormal trophoblastic proliferation histologically. It is characterized by trophoblastic implantation into the myometrium with abundant colored flows of low resistance, which are caused by focal or diffuse dilatation of pelvic vessels and arteriovenous fistulas [38]. Shan et al. [12] reported a misdiagnosis of choriocarcinoma and indicated the difficulty in distinguishing intramural pregnancy from choriocarcinomas. A laparotomy was performed to confirm the diagnosis of intramural pregnancy. During the procedure, the lesion was excised followed by initial unsatisfactory treatment with MTX-based chemotherapy. Memtsa et al. [24] reported a patient who underwent ultrasound-guided biopsy to exclude the possibility of invasive trophoblastic disease. Other than two-dimensional ultrasound, other imaging modalities that are alternatively used are MRI, which has a diagnostic accuracy of 96% [39]. Three-dimensional ultrasound is better in delineating the location of the mass and the relationship between the mass and the uterine cavity before it ruptures [3, 6, 40]. One patient underwent three-dimensional sonography that showed the sinus connecting the sac with the endometrial cavity [26].

Management of intramural pregnancies should be individualized. Treatments for intramural pregnancy differ based on the location of the conceptions, patient's condition, gestational age and the desire to maintain fertility [3, 24]. Commonly available management options include expectant, medicinal and surgical treatment. Helene et al. reported a patient with mild clinical symptoms (left lower abdominal pain and slight vaginal bleeding), no evidence of uterine

rupture and 9.5 mIU HCG levels who opted for expectant management due to the patients' desire for future fertility. Follow-up ultrasound images 8 days later confirmed a failed pregnancy [2]. Sentilhes et al. proposed that expectant management could be a viable option for patients who are stable (asymptomatic, narrow crown-rump length and the absence of cardiac activity) [41]. However, women with a gestational sac at or beyond the second trimester are prone to massive peritoneal effusion and hemorrhagic shock. In these cases, hysterotomy and resection is the preferred choice [22]. Topical or systemic administration of methotrexate is the most common treatment strategy, with or without injection of intracardiac potassium chloride [39]. Previous studies have demonstrated that there was no correlation between methotrexate administration and post-surgical spontaneous abortions or the incidence of congenital anomalies. Mylene et al. suggested that symptom-free women with gestational diameter < 2 cm, absence of fetal cardiac activity and serum HCG level < 2000 mIU/ml should be administered methotrexate [42]. Review of the cases in this study suggests that when HCG levels were high and color ultrasound indicated abundant peripheral blood flow, MTX was generally considered.

Minimally invasive management has been widely accepted [25]. Real-time laparoscopic findings suggest that the round ligament could be a valid boundary marker for medial intramural pregnancy and lateral interstitial conceptus [43]. Ana et al. conducted a prospective trial to demonstrate that laparoscopy was superior to laparotomy. This was based on the duration of surgery, bleeding volume and pregnancy outcome [44]. In addition to routine laparoscopic/transabdominal excision, and even hysterectomy caused by uterine rupture, uterine artery embolization and temporary balloon occlusion have been demonstrated to achieve embryo atrophy and absorption. Transfemoral temporary aortic balloon occlusion has the advantage for safety and efficacy but has a high risk of bleeding [21, 45]. One study reported that ultrasound detection of sinus connecting the embryo sac and cavity induced hysteroscopic excision [26]. Precise treatment not only brings relief to patients and reduces their anxiety for surgery, but also helps ultrasound operators to make accurate diagnosis.

Conclusion

This case and review of the literature highlights the challenges of diagnosing intramural ectopic pregnancy. Unremarkable clinical characteristics, operator inexperience (due to the rareness of intramural pregnancies) and indistinguishable imaging features are major challenges for sonographers and gynecologists. Better understanding of the ultrasound diagnostic criteria, flexible and comprehensive application of various available radiological techniques such as TVS/TAS (including CDFI, PDI), three-dimensional ultrasound and MRI (as necessary) may help with detecting, diagnosing and treatment of intramural pregnancies. Gynecologists should be able to incorporate ultrasound reports with clinical examinations for selecting suitable treatment options.

In conclusion, communication and cooperation between sonographers and gynecologists are vital for proper diagnosis and treatment of intramural pregnancies.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

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Research involving human participants All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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