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Imaging in gynecological disease (25): clinical and ultrasound characteristics of intramural pregnancy

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KEYWORDS: diagnosis; ectopic pregnancy; intramural pregnancy; management; ultrasound imaging

CONTRIBUTION

What are the novel findings of this work?
Intramural pregnancy is a rare form of ectopic pregnancy, on which there is little published literature regarding the diagnosis, management or natural history. In this large series of patients, we describe the different morphological appearances on ultrasound of both partial and complete intramural pregnancy and the different management approaches.

What are the clinical implications of this work?
Accurate early diagnosis of intramural pregnancy and better understanding of the efficacy of conservative and surgical management options is important for patient counseling. Familiarity with morphological findings on ultrasound examination and key diagnostic criteria should facilitate early detection of intramural pregnancy and lead to better patient care.

ABSTRACT

Objective *To describe the clinical and sonographic characteristics of intramural pregnancy, as well as the available management options and treatment outcomes.*

Methods *This was a retrospective single-center study of consecutive patients with a sonographic diagnosis of intramural pregnancy between November 2008 and November 2022. An intramural pregnancy was diagnosed on ultrasound when a pregnancy was implanted within the uterine corpus, above the level of the internal cervical os and separate from the interstitial section of the Fallopian tube, and extended beyond the decidual–myometrial junction. Clinical, ultrasound, relevant surgical and histological information and outcomes were retrieved from each patient's record and analyzed.*

Results *Eighteen patients were diagnosed with an intramural pregnancy during the study period. Their median age was 35 (range, 28–43) years and the median gestational age at diagnosis was 8 + 1 (range, 5 + 5 to 12 + 0) weeks. Vaginal bleeding with or without abdominal pain was the most common presenting symptom, recorded in eight patients. Nine (50%) patients had a partial and nine (50%) had a complete intramural pregnancy. Embryonic cardiac activity was present in eight (44%) pregnancies. The majority of pregnancies (n = 10 (56%)) were initially managed conservatively, including expectant management in eight (44%) cases, local injection of methotrexate in one (6%) and embryocide in one (6%). Conservative management was successful in nine of the 10 (90%) pregnancies, with a median time to serum human chorionic gonadotropin resolution of 71 (range, 35–143) days. One patient with an ongoing live pregnancy had an emergency hysterectomy for a major vaginal bleed at 20 weeks' gestation. No other patient managed conservatively experienced any significant complication. The remaining eight (44%) patients had primary surgical treatment, comprising transcervical suction curettage in seven (88%) of these cases, while one patient presented with uterine rupture and underwent emergency laparoscopy and repair.*

Conclusions *We describe the ultrasound features of partial and complete intramural pregnancy, demonstrating key diagnostic features. Our series suggests that, when intramural pregnancy is diagnosed before 12 weeks' gestation, it can be managed either conservatively or by surgery, with preservation of reproductive function in most women.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

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INTRODUCTION

Aim

The aim of this study was to describe the clinical and sonographic characteristics of intramural pregnancy, as well as the available management options and treatment outcomes.

Background

Epidemiology

The estimated incidence worldwide of ectopic pregnancy (of which more than 90% are located within the Fallopian tube) is 1–2%[1]. The published literature on intramural pregnancy is limited to just 56 cases[2]. However, the apparent rarity of these pregnancies may reflect the difficulty of their diagnosis rather than their true incidence.

The first description of intramural pregnancy, in 1913, reported a case of trophoblastic cells implanted into a foci of adenomyosis[3]. In the 1990s, the first non-invasive diagnosis was made by ultrasound prior to surgery[4]. More recently, Memtsa *et al.*[5] focused on intramural pregnancy as a distinct entity, separate from Cesarean scar and cervical ectopic pregnancy.

Clear agreement on the definition and description on ultrasound of different types of ectopic pregnancy was lacking in the wider international gynecological community until 2020, when the European Society of Human Reproduction and Embryology (ESHRE) working group on Ectopic Pregnancy provided a comprehensive classification[6]. Their recommendation was that cervical, Cesarean scar and intramural pregnancies should be classified as uterine ectopic pregnancy, defined as a pregnancy located within the uterus but which breaches the decidual–myometrial junction and extends into the myometrium. They further subclassified intramural pregnancy into complete or partial, depending on whether, on ultrasound examination, the pregnancy is confined completely to the myometrium (complete) or has a visible communication with the endometrial cavity (partial)[6]. In the series described herein, we have used the definition proposed by the ESHRE working group[6]. In contrast to Cesarean scar or cervical pregnancy, both of which have a defined location of implantation within the uterus, the implantation site of an intramural pregnancy may be anywhere in the uterine corpus.

The etiology of intramural pregnancy is assumed to be implantation of the blastocyst and development of the placenta beyond the decidual–myometrial junction. Any form of surgical trauma to the uterine corpus, such as myomectomy, hysteroscopic surgery or transcervical evacuation of products of conception, could result in a residual myometrial defect, facilitating intramural implantation[7]. In this respect, the etiology is similar to those of Cesarean scar pregnancy and cervical ectopic pregnancy, which are also caused by previous surgical trauma. However, defects in the myometrium could also be due to acquired conditions, such as adenomyosis[3], or to a congenital uterine anomaly.

Microscopy

Microscopically, intramural pregnancies demonstrate the presence of villous tissue within the myometrium. On histological section, partial intramural pregnancies show chorionic villi and decasualized endometrium. In contrast, in complete intramural pregnancy, chorionic villi are found surrounded by myometrium only[2].

Histological examination can thus aid in confirming the diagnosis, but it is not essential for diagnosis, as many intramural pregnancies are managed conservatively. Furthermore, in many centers, pregnancy tissue sent for histological analysis is examined only to confirm the presence of products of conception and to exclude gestational trophoblastic disease (GTD), which means that only a small number of sections from the entire tissue are analyzed, so myometrial tissue is easily missed. The reference standard for diagnosis of intramural pregnancy should, therefore, be ultrasound.

Macroscopy

Macroscopically, the appearance of intramural pregnancy varies, ranging from a heterogonous solid lesion to a gestational sac with or without embryo or cardiac activity. The pregnancy is located within the uterine corpus above the level of the internal cervical os and separate from the interstitial tube, and, most importantly, implantation extends beyond the decidual–myometrial junction[6]. This can result in a partial intramural pregnancy, in which part of the pregnancy extends into the endometrial cavity, or a complete intramural pregnancy, in which the pregnancy is implanted entirely within the myometrium, without visible communication with the endometrial cavity.

Clinical symptoms and prognosis

Intramural pregnancy is a diagnostic challenge for two reasons. First, it is so rare that most early-pregnancy clinicians have no or minimal experience of the condition. Second, the presenting symptoms are non-specific (usually bleeding and/or pain) [8]. Thus, it is rare that the diagnosis is considered. In some cases, suspicion may be aroused by an unsuccessful attempt at evacuation of a presumed normally sited pregnancy.

An early-pregnancy ultrasound scan should always start with an assessment of the cervix, following the endocervical canal to the uterine cavity. Assuming that a pregnancy is visualized within the cavity, the decidual–myometrial junction should then be assessed to detect extension into the myometrium. If the uterine cavity is empty, then, as well as looking for an extrauterine ectopic pregnancy, the operator should assess the myometrium for a visible pregnancy.

A suspected pregnancy within the myometrium may be seen clearly due to the visible gestational sac with yolk

sac, embryo or even cardiac activity. However, a solid heterogeneous mass may be difficult to differentiate from other uterine pathology, such as adenomyotic cysts or cystic fibroids, which may mimic pregnancy structures. The key feature to help facilitate diagnosis is increased blood flow around an intramural pregnancy[9].

The majority of published case reports describe surgical or medical management of intramural pregnancy, with only three cases managed expectantly, so little is known about the natural history of intramural pregnancy that is managed expectantly[10–12]. In considering the potential risks to the patient associated with different management options, whether the pregnancy is live or failed, partial or complete, and the extent of myometrial involvement are important factors. a live partial intramural pregnancy could potentially reach viability, but the patient must be informed about the risk of uterine rupture and abnormally adherent placenta, both of which may cause massive obstetric hemorrhage requiring life-saving hysterectomy to secure hemostasis. However, in the absence of strong evidence regarding these risks, decisions whether to terminate or continue the pregnancy are very difficult and must be made on a case-by-case basis. In cases of complete live intramural pregnancy, the placenta develops entirely within the uterine muscle and the risk of rupture is likely to be higher compared with that of partial intramural pregnancy, in which the placenta may grow at least partially within the uterine cavity. There has been no case published of a complete intramural pregnancy resulting in a live birth.

METHODS

This was a retrospective single-center study of consecutive patients diagnosed with an intramural pregnancy on ultrasound. Patients were identified retrospectively from a cohort of pregnant patients attending the Early Pregnancy Assessment Unit at University College London Hospital (UCLH) between November 2008 and November 2022. All ultrasound examinations were carried out transvaginally and, in most cases, also transabdominally, by an experienced operator using high-resolution ultrasound equipment with two-dimensional (2D) and three-dimensional (3D) diagnostic modalities (Voluson 730 and E8 Expert, GE Healthcare, Zipf, Austria). In all cases, the diagnosis was confirmed by a level-III ultrasound examination. An intramural pregnancy was diagnosed on transvaginal and/or transabdominal ultrasound if it was implanted within the uterine corpus above the level of the internal cervical os and separate from the interstitial section of the Fallopian tube, and breached the decidual–myometrial junction[6]. Management was individualized, according to gestational age at diagnosis, clinical symptoms, type of intramural pregnancy (complete or partial), serum human chorionic gonadotropin (hCG) levels and the patient's preferences. hCG resolution time was defined as the number of days from presentation to the point at which hCG declined to prepregnancy levels (< 20 IU/L). Pregnancy resolution time was the interval between presentation and the day on which the pregnancy tissue was reduced in size so much that it became non-detectable on ultrasound.

Patients' demographic data, previous obstetric and gynecological history, clinical findings, ultrasound data and images and symptoms at the time of the first examination were recorded and stored in a our clinical database (Viewpoint Version 5, Bildverargeritung GmbH, Munich, Germany). Pregnancies were dated according to the last menstrual period. A standard Kurtosis analysis indicated that some values were not normally distributed, so these data are presented as median and range. The protocol was approved and consent was waived as all ultrasound records were examined within the center and basic clinical data were collected using a standard anonymized clinical audit protocol. Ethical committee approval (UK NHS Health Research Authority Research Ethical committee approval reference 18/WM/0328) was obtained prior to the start of this study.

RESULTS

During the study period, 18 patients were diagnosed with an intramural pregnancy. Table 1 presents the patient characteristics. Indications for the initial visit to our early pregnancy unit are given in Table 2. Ten (56%) women were referred from their local hospital for a second opinion, due to suspicion of an ectopic pregnancy in five, because of unsuccessful surgical evacuation of an initially presumed normally sited pregnancy in four and because of suspicion of an ectopic pregnancy after unsuccessful surgical evacuation of an initially presumed normally sited pregnancy in one case. Two were referred following

Table 1 Key demographics of patients diagnosed with intramural pregnancy ($n = 18$)

Characteristic	*Value*
Age (years)	35 (28–43)
Gravidity	3 (1–9)
Parity	0 (0–3)
Gestational age at presentation (weeks)	8 + 1 (5 + 5 to 12 + 0)
Previous termination of pregnancy	1 (6)
Previous miscarriage	11 (61)
Previous vaginal delivery	6 (33)
Previous Cesarean section	2 (11)

Data are given as median (range) or *n* (%).

Table 2 Indications for initial visit to early pregnancy unit in patients with intramural pregnancy ($n = 18$)

Indication	n *(%)*
Unsuccessful attempted evacuation of presumed normally sited pregnancy	6 (33)
Vaginal bleeding and abdominal pain in first trimester	4 (22)
Vaginal bleeding in first trimester	4 (22)
Suspected miscarriage on first-trimester scan	2 (11)
Abdominal pain in first trimester	1 (6)
Reassurance scan	1 (6)

unsuccessful medical management with methotrexate. Two of the eighteen women had conceived via *in-vitro* fertilization. No patient had a history of prior intramural pregnancy, but one had a history of a previous partial interstitial pregnancy managed by transcervical suction evacuation.

Fourteen (78%) patients had a history of previous uterine surgery (Table 3). In five (28%) patients, our ultrasound examination identified concomitant uterine pathology, including uterine fibroids and adenomyosis. Four patients had no identifiable risk factors for an intramural pregnancy.

Ultrasound findings

A conclusive diagnosis of intramural pregnancy was made at our initial ultrasound examination in 9/18 (50%) patients. In the remaining nine cases, follow-up visits were required to reach a certain diagnosis, as, initially, the pregnancy was misdiagnosed as normally sited ($n = 3$) or an interstitial pregnancy ($n = 2$), or the implantation site was not clear on the first scan ($n = 4$).

In 13/18 (72%) cases, a gestational sac was visible, of which 10 contained an embryo (eight with a heartbeat), one contained a yolk sac only and two were empty sacs. The other five (28%) cases showed solid trophoblast only. Diagnosis of a complete intramural pregnancy was made in 9/18 (50%) cases (Figure 1) and a partial one was diagnosed in 9/18 (50%) cases (Figure 2).

Table 3 Summary of risk factors for intramural pregnancy in 18 cases with this diagnosis

Case	*Number of risk factors*	*Details*
1	2	Suction evacuation, laparoscopic myomectomy
2	0	N/A
3	2	Fibroids, laparoscopic myomectomy
4	0	N/A
5	1	Cesarean section
6	3	Suction evacuation × 2, manual removal of placenta
7	4	Suction evacuation × 3, diagnostic hysteroscopy
8	2	Adenomyosis, manual removal of placenta
9	1	Suction evacuation
10	1	Suction evacuation
11	0	N/A
12	0	N/A
13	4	Fibroids, laparoscopic myomectomy, open myomectomy, and laparotomy and repair of uterine rupture at 17 weeks' gestation
14	4	Fibroids, suction evacuation, Cesarean section, laparoscopic myomectomy
15	1	Open myomectomy
16	4	Fibroids, adenomyosis, laparoscopic myomectomy, open myomectomy
17	1	Suction evacuation
18	2	Manual removal of placenta, operative hysteroscopy

N/A, not applicable.

Figures 3 and 4 demonstrate intramural pregnancies presenting with gestational sac and live embryo. Figures 5 and 6b show failed intramural pregnancies with inhomogeneous pregnancy tissue within the myometrium. In one patient there was only a very small area of hyperechoic vascular tissue within the posterior myometrium, without connection to the cavity or a visible gestational sac (Case 16). This case had been particularly challenging to diagnose as the patient had multiple fibroids distorting the posterior myometrium.

In 11/18 (61%) patients, the pregnancy was found close to, but separate from, the interstitial portion of the Fallopian tube. The gestational sac was implanted below the interstitial tube in eight of these cases; Figure 7c

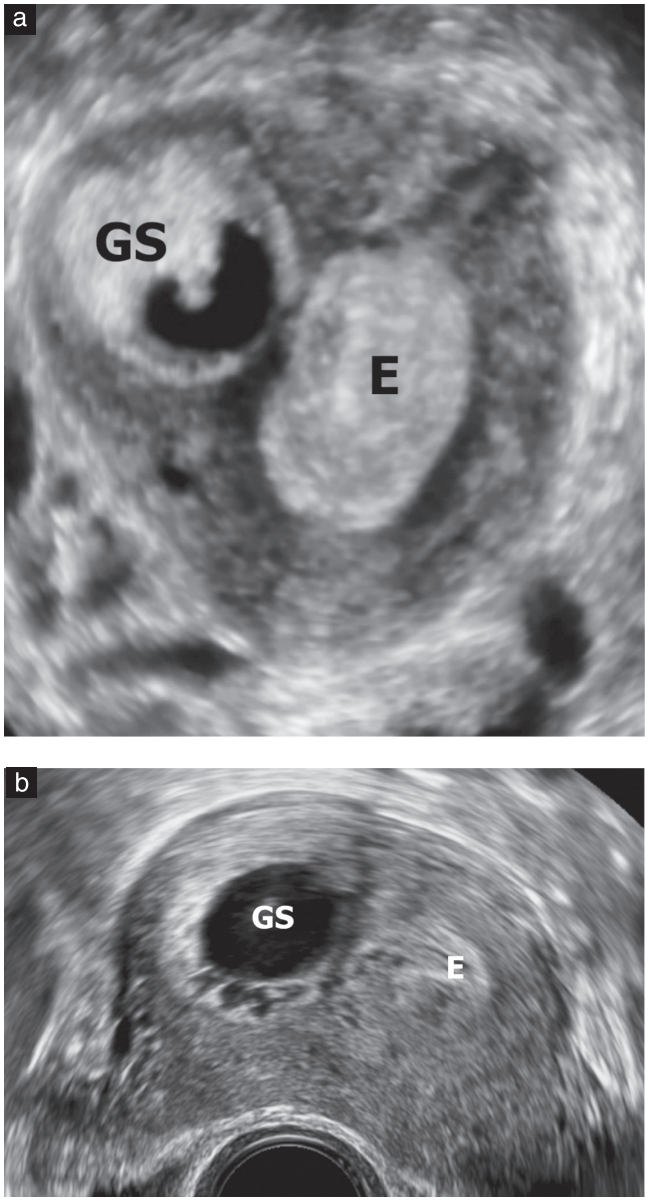

Figure 1 Three-dimensional coronal view (a) and transverse section (b), showing endometrial cavity (E) and gestational sac (GS) within myometrium of right uterine wall, in keeping with complete intramural pregnancy. This case was managed successfully with local methotrexate injection.

demonstrates the location of the pregnancy in one of two such cases. The pregnancy was above the interstitial tube in two of the 11 cases, as shown in the example in Figure 8a. In one case, neither interstitial tube was clearly visualized, due to severe distortion of the uterine anatomy caused by previous open myomectomy.

The patients' intended treatment options and the final treatment required are shown in Figure 9. Ten of the 18 (56%) patients were managed conservatively initially, eight undergoing expectant and two medical management. Of the eight that were managed expectantly initially, six (75%) were managed successfully either to resolution of the pregnancy on ultrasound or to a sustained decline in hCG levels at the time of writing (Table 4). Of the two women with unsuccessful expectant management, one, who had elected to continue with the pregnancy after diagnosis, required an emergency hysterectomy at 20 weeks' gestation due to uncontrollable heavy vaginal bleeding. One patient underwent a diagnostic laparoscopy for increasing lower abdominal pain and rising hCG levels (from

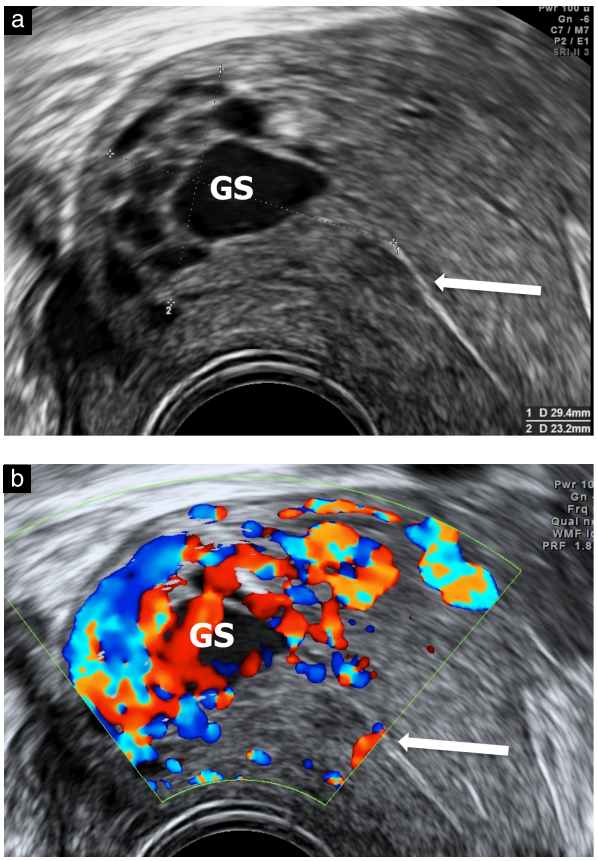

Figure 2 Longitudinal section of uterus on grayscale (a) and color Doppler (b) imaging, showing endometrial cavity (arrow) and gestational sac (GS) embedded deeply in myometrium of upper left of cavity, in keeping with partial intramural pregnancy. Calipers in (a) indicate complete pregnancy tissue. On color Doppler examination (b), GS was highly vascularized.

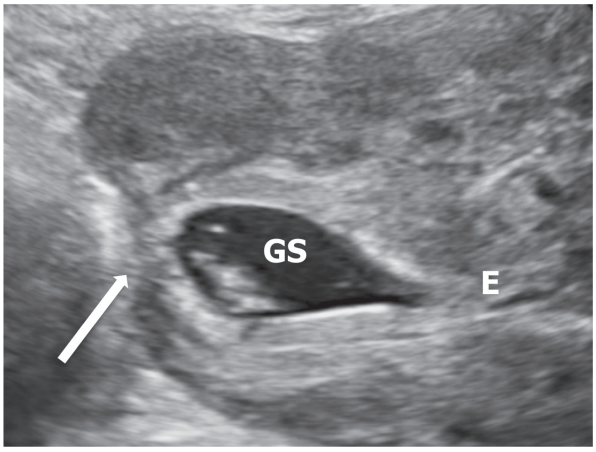

Figure 3 Longitudinal section of uterus in partial intramural pregnancy, showing endometrial cavity (E) and gestational sac (GS) with live embryo within right lateral myometrium. Note very thin layer of myometrium covering GS (arrow).

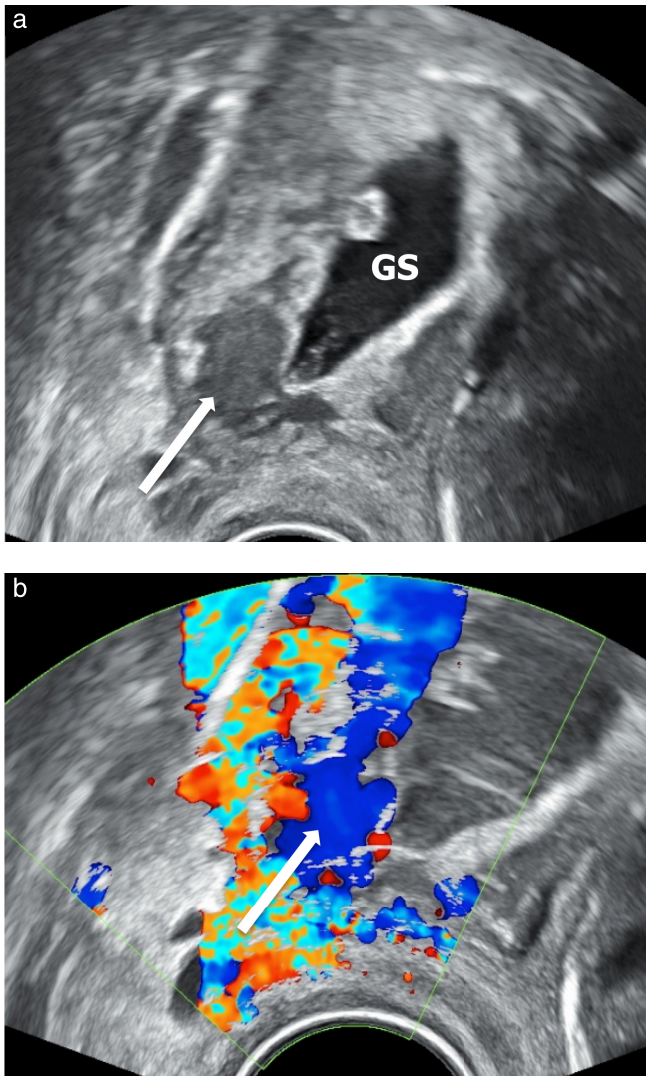

Figure 4 (a) Longitudinal section of uterus showing gestational sac (GS) with live 7-week embryo in partial intramural pregnancy, with placenta invading deep into posterior myomyometrium and placental lacunae (arrow). (b) Color Doppler image showing arteriovenous fistula leaking into large lake in lower right part of placenta (arrow).

398 IU/L to 1563 IU/L after 4 weeks). Intraoperatively, there was no evidence of hemoperitoneum and 10 mg methotrexate was injected into the placental tissue under continuous transvaginal ultrasound guidance, following which, the hCG level returned to prepregnancy levels after 6 weeks.

One patient with a small live pregnancy underwent embryocide. She complained of increasing abdominal discomfort during follow-up and her hCG levels were rising (from 25 222 IU/L to 34 896 IU/L over 1 week). She was therefore given 25 mg local methotrexate injection, after which her symptoms subsided and her hCG levels declined uneventfully.

One patient (Case 1) requested medical treatment with local methotrexate as she felt that expectant management would require longer to complete.

Of the 10 patients who were initially managed conservatively, two did not have follow-up of hCG level and all of the remaining eight (100%) had successful resolution of the pregnancy, defined as resolution of hCG, with a median time to hCG resolution of 71 (range, 35–143) days. Three were still being followed up for pregnancy resolution time at the time of writing, four did not have a scan to assess resolution of the pregnancy and the remainder had a median pregnancy resolution time of 214 (range, 63–535) days.

Nine of the 18 (50%) patients underwent surgical management, eight having primary surgical treatment and the one managed expectantly initially who had secondary emergency surgical treatment for heavy vaginal bleeding (Case 10). In three cases, patients were assessed as being at high risk of uterine rupture if the pregnancy progressed, based on the location of implantation of the pregnancy, and were advised to have surgery, in one case there was evidence of uterine rupture during ultrasound assessment and in four cases, the patient opted for surgical management after discussion of the available treatment options. Seven (88%) of these had a partial intramural pregnancy, which was accessible vaginally, so transcervical suction evacuation was possible (two as emergencies). All operations were carried out under continuous ultrasound guidance. There was no case of uterine perforation. Three surgical cases required insertion of a cervical suture to secure hemostasis by creating an intrauterine hematoma to exert tamponade, as is carried out routinely with Cesarean scar ectopic pregnancy.

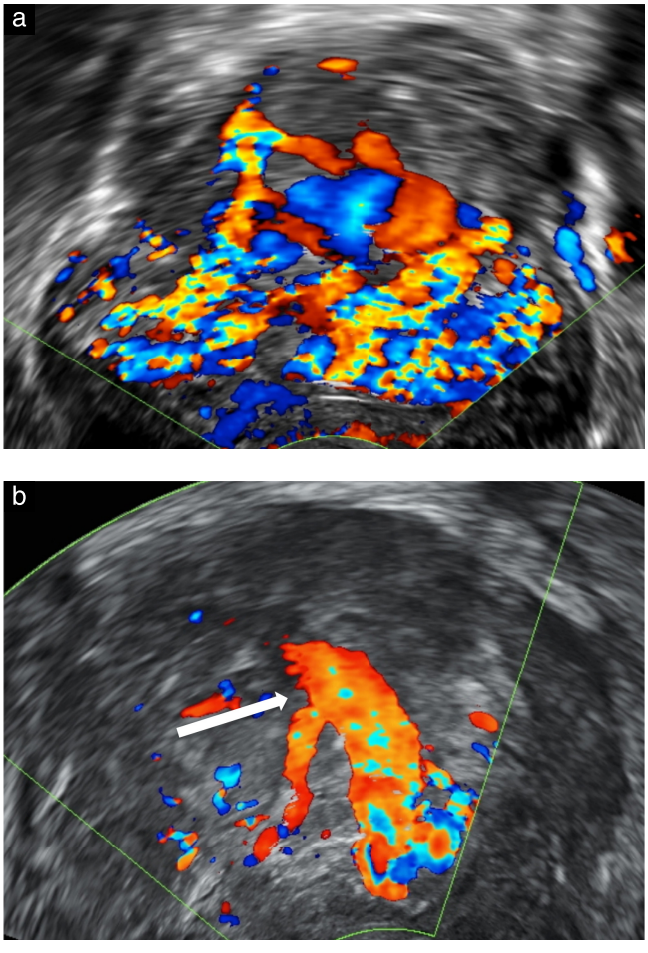

Figure 5 (a) Color Doppler image showing extremely vascular, thickened, irregular posterior uterine wall, in partial intramural pregnancy. No discrete trophoblast is discernible. (b) Color Doppler image showing single large blood vessel (arrow) delivering blood directly from uterine artery to retained pregnancy tissue in posterior myometrium, after patient had undergone uterine artery embolization prior to emergency surgery.

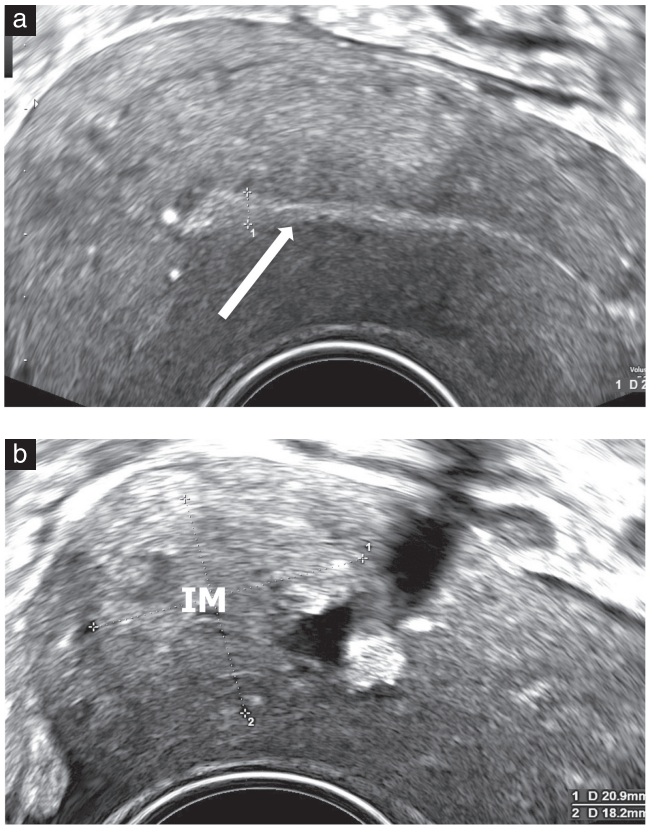

Figure 6 (a) Longitudinal section of uterus showing empty uterine cavity and thin endometrium (arrow and calipers). (b) Cluster of inhomogeneous pregnancy tissue (IM and calipers) within left fundal myometrium, in keeping with diagnosis of failed intramural pregnancy.

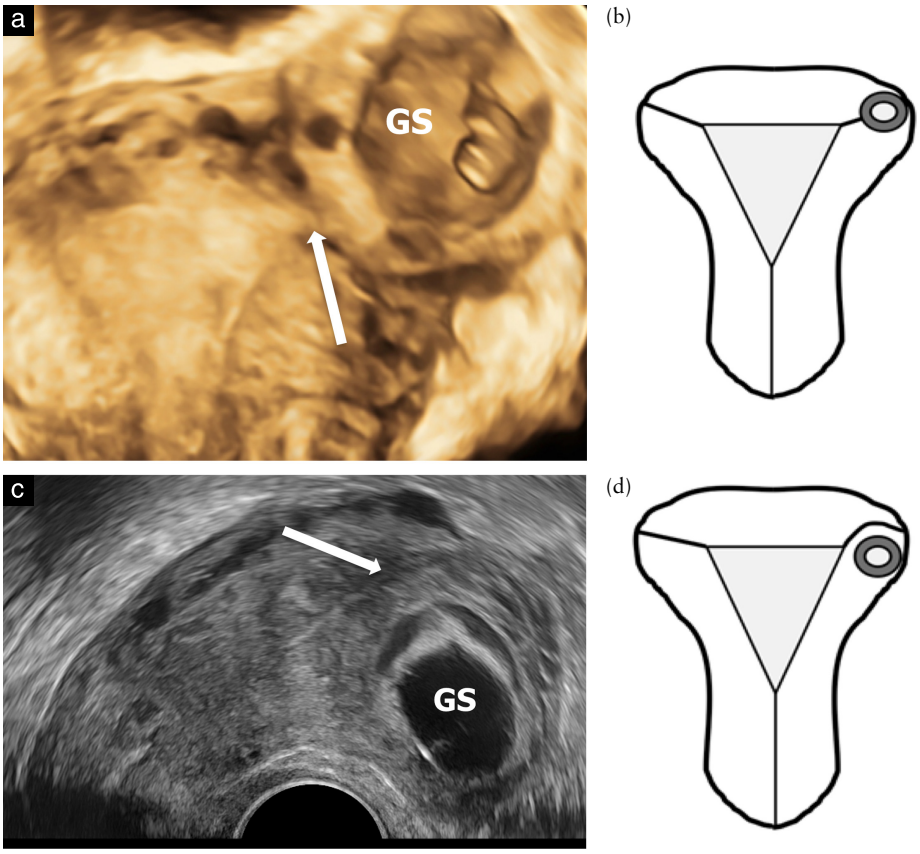

Figure 7 Comparison of interstitial (a,b) and intramural (c,d) ectopic pregnancy. (a) Three-dimensional ultrasound image showing uterine cavity and gestational sac (GS) containing live embryo implanted within interstitial portion of left Fallopian tube (arrow), in keeping with complete interstitial pregnancy. (b) Schematic diagram of complete interstitial pregnancy. (c) Two-dimensional ultrasound image of GS implanted in anterior myometrium, with interstitial portion (arrow) clearly seen above the pregnancy, in keeping with complete intramural pregnancy. (d) Schematic diagram of complete intramural pregnancy.

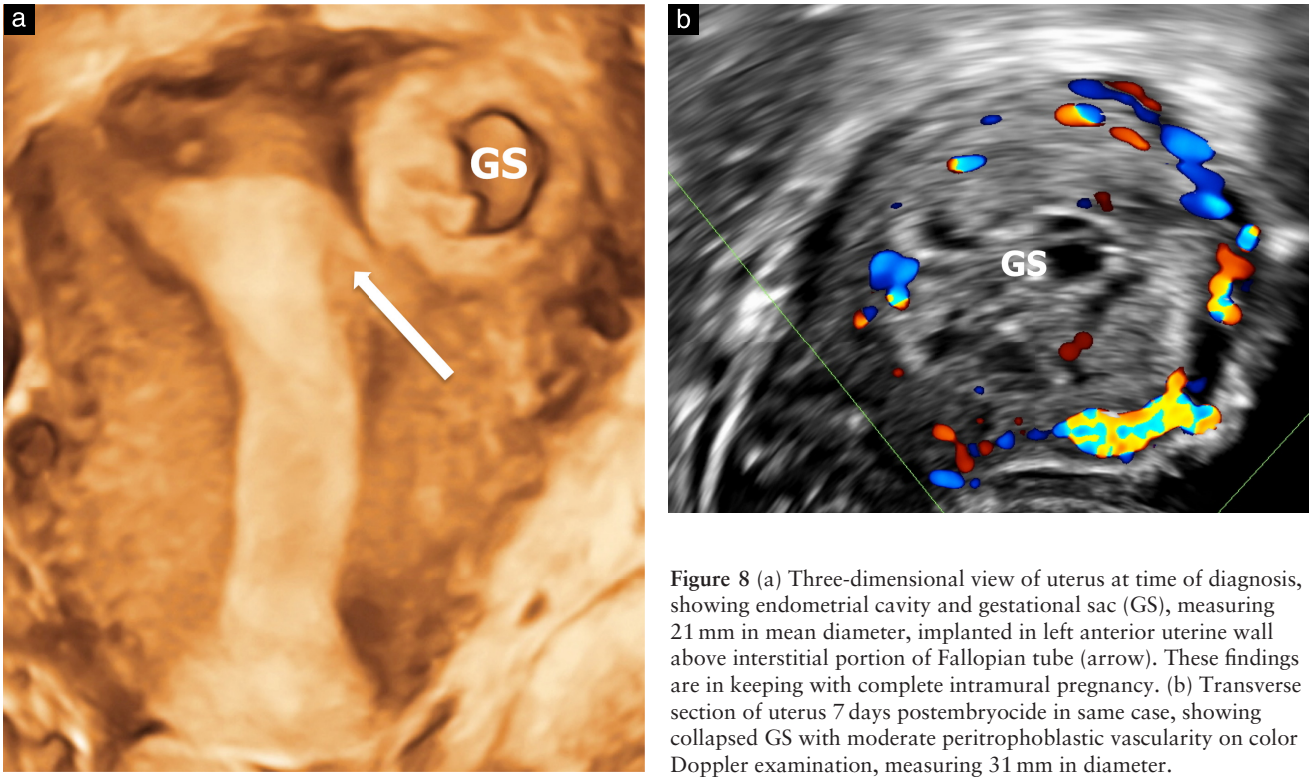

Figure 8 (a) Three-dimensional view of uterus at time of diagnosis, showing endometrial cavity and gestational sac (GS), measuring 21 mm in mean diameter, implanted in left anterior uterine wall above interstitial portion of Fallopian tube (arrow). These findings are in keeping with complete intramural pregnancy. (b) Transverse section of uterus 7 days postembryocide in same case, showing collapsed GS with moderate peritrophoblastic vascularity on color Doppler examination, measuring 31 mm in diameter.

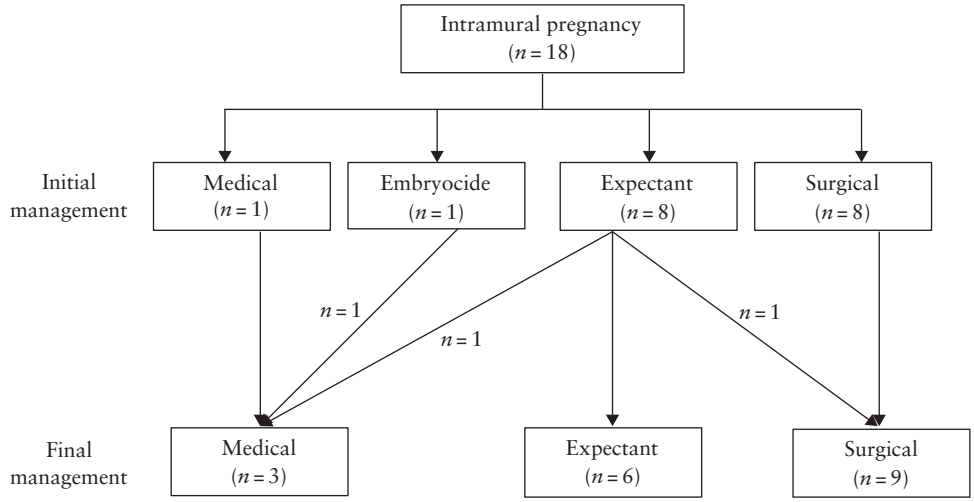

Figure 9 Flowchart summarizing initial and final management of 18 patients with intramural pregnancy.

Table 4 Eighteen cases of intramural pregnancy managed conservatively ($n = 10$) or surgically ($n = 8$)

Case	*Type of pregnancy*	*Mean GS/tissue diameter* (mm)*	*CRL (mm)*	*ECA*	*hCG at diagnosis (IU/L)*	*Initial treatment*	*hCG resolution time (days)*	*Pregnancy resolution time (days)*	*Complications*
1	Complete	19.3	6.2	+	35 119	Local MTX	84	214	None
2	Complete	8†	N/A	N/A	1159	Expectant	42	DNA	Increasing pain and hCG, laparoscopy, local MTX
3	Complete	7.3	N/A	N/A	4028	Expectant	35	63	None
4	Complete	10.9	3.6	+	25 222	Embryocide	106	535	Increasing pain and hCG, local MTX
5	Complete	20†	N/A	N/A	N/A	Expectant	DNA	DNA	Unknown, presumed none
6	Complete	18	N/A	N/A	5739	Expectant	69	F/U ongoing	None
7	Complete	27.3	16.1	–	2742	Expectant	72	F/U ongoing	None
8	Complete	29	13.2	–	731	Expectant	143	F/U ongoing	None
9	Partial	26†	N/A	N/A	1693	Expectant	57	DNA	None
10	Partial	37.3	38.1	+	N/A	Expectant	N/A	N/A	Heavy vaginal bleeding requiring emergency hysterectomy
11	Complete	40.0	24.4	+	58 755	Emergency laparoscopy, uterine rupture, repair	N/A	N/A	Preoperative rupture, EBL 2.1 L, transfusion of 3 units of blood
12	Partial	38.3	N/A	N/A	130	Suction evacuation	N/A	N/A	None
13	Partial	26	11.0	+	N/A	Suction evacuation	N/A	N/A	None
14	Partial	30.3	9.6	+	N/A	Emergency suction evacuation and insertion of cervical suture	N/A	N/A	Heavy vaginal bleeding prior to planned procedure, EBL 3.2 L (pre- and intra-operatively), transfusion of 5 units of blood, admitted to ICU
15	Partial	28.7	16.9	+	165 903	Diagnostic laparoscopy, suction evacuation	N/A	N/A	None
16	Partial	32†	N/A	N/A	584	Emergency suction evacuation and insertion of cervical suture	N/A	N/A	Heavy bleeding and syncope whilst awaiting surgery
17	Partial	22.0	15.5	+	N/A	Suction evacuation and insertion of cervical suture	N/A	N/A	None
18	Partial	39†	N/A	N/A	N/A	Suction evacuation	N/A	N/A	None

Case 5 had retained pregnancy tissue post first-trimester miscarriage; human chorionic gonadotropin (hCG) was not required at diagnosis and patient did not attend (DNA) her planned follow-up appointment. In Case 10, hCG levels were not taken at diagnosis as patient was committed to continuing the pregnancy. *Mean of three perpendicular diameters. †Solid pregnancy tissue. CRL, crown–rump length; EBL, estimated blood loss; ECA, embryonic cardiac activity; F/U, follow-up; GS, gestational sac; ICU, intensive care unit; MTX, methotrexate; N/A, not applicable.

One of the emergency surgical procedures was performed because of symptomatic heavy bleeding whilst awaiting surgery, despite the patient already having undergone uterine artery embolization (UAE) (Figure 5, Case 16). The other emergency case had been scheduled as a semi-elective procedure, but, 2 days prior to the planned surgery, the patient presented with very heavy bleeding.

In the one complete intramural pregnancy managed surgically, ultrasound diagnosis of a live, complete intramural pregnancy was made when the patient presented at 10 weeks' gestation with heavy bleeding and pain. The pregnancy was seen to be rupturing through the posterior uterine wall, below the left Fallopian tube. An emergency laparoscopic evacuation of the ruptured intramural pregnancy was performed, with repair of the uterine defect. The estimated blood loss was 2.1 L.

All histological examinations were performed by a team of consultant histopathologists with an interest in gynecological pathology and samples all showed evidence of normal chorionic villi and no atypical trophoblastic proliferation.

Five of the cohort of eighteen women are known to have had a subsequent pregnancy, including two term deliveries and two complicated by early pregnancy failure, while one presented with a Cesarean scar ectopic pregnancy, which required surgical management.

DISCUSSION

This study presents the largest series to date of patients diagnosed with an intramural pregnancy and managed in a single center. We recorded 18 cases over a period of 14 years, which suggests that intramural pregnancy is probably more common than previously thought. This is also supported by the fact that only 1 of 10 cases referred to us for expert opinion had the diagnosis of intramural pregnancy suspected by their referring hospital, with five cases referred as a suspected cornual, Cesarean scar, cervical or interstitial ectopic pregnancy, confirming that clinicians are often unfamiliar with intramural pregnancy. It is likely, therefore, that many cases of intramural pregnancy go undiagnosed and thus that the condition is underreported.

Risk factors

We found that 78% of patients had a history of prior uterine trauma, confirming this as the main risk factor for the development of an intramural pregnancy. In addition, 11% had evidence of adenomyosis, which may have predisposed them to intramural implantation. This is similar to findings of previously published studies which showed that 76–100% of patients diagnosed with intramural pregnancy had identifiable risk factors, with the most common reported as dilatation and curettage and adenomyosis[7, 13, 14]. These data suggest that most intramural pregnancies are a consequence of primary or secondary loss of the normal anatomy of the uterine corpus, allowing the blastocyst to implant within the myometrium.

Ultrasound diagnosis

All eighteen cases in this series were diagnosed using 2D and 3D ultrasound. In 11/18 (61%) cases, 3D ultrasound provided critical information which helped differentiate between interstitial and intramural pregnancy. 3D ultrasound has been reported as providing more accurate localization of the gestational sac than is possible with 2D ultrasound, as use of multiple scan planes allows better visualization of the decidual–myometrial junction, which is often affected by adenomyosis, making diagnosis challenging[15,16]. Other studies have used MRI to confirm the diagnosis, as multiplanar images allow delineation of the location of the gestational sac in relation to the endometrial cavity[17,18]. MRI has also been reported as a useful modality in differentiating between an intramural pregnancy and suspected GTD or degenerating fibroids[17]. In a recently published literature review[19], of the 18 cases described, four required MRI in addition to ultrasound to aid the diagnosis of intramural pregnancy. However, this was not necessary in any of our cases, indicating that ultrasound examination performed by an expert operator using a standardized protocol can diagnose an intramural pregnancy reliably.

The key features of intramural pregnancy on ultrasound are the presence of a gestational sac with a live fetus or heterogeneous solid placental tissue completely or partially within the myometrium of the uterine corpus, separate from any Cesarean section scar or the interstitial portion of the Fallopian tube.

Differential diagnosis

Differentiating an intramural pregnancy from an interstitial pregnancy requires visualization and assessment of the interstitial tube. In interstitial pregnancy, the interstitial line is interrupted by the pregnancy (Figure 7a,b). In contrast, in intramural pregnancy located near the interstitial tube, the interstitial line is displaced rather than interrupted by the pregnancy, such that it often appears curved and elongated (Figure 7c,d). This may be assessed more clearly on 3D than on 2D ultrasound, as demonstrated in Figure 10[20].

Uterine pathology may make the diagnosis of intramural pregnancy on ultrasound more challenging. For example, in two patients referred to our hospital with suspected heterotopic intramural pregnancy, the final diagnoses were in fact an adenomyotic cyst (Figure 11) and a degenerating cystic fibroid (Figure 12). The lack of trophoblastic reaction and minimal Doppler vascularity are key indicators that differentiate these lesions from intramural gestations.

Partial intramural pregnancy is easily misdiagnosed as normally sited pregnancy if the pregnancy expands into the cavity (Figure 3) and no assessment is made for extension of the pregnancy beyond the decidual–myometrial

junction. A failing partial intramural pregnancy may be evacuated successfully with transcervical suction. However, when most of the placental tissue is implanted deeply inside the myometrium, a suction procedure done with no ultrasound guidance or additional hemostatic measures may result in excessive bleeding or retained placental tissue.

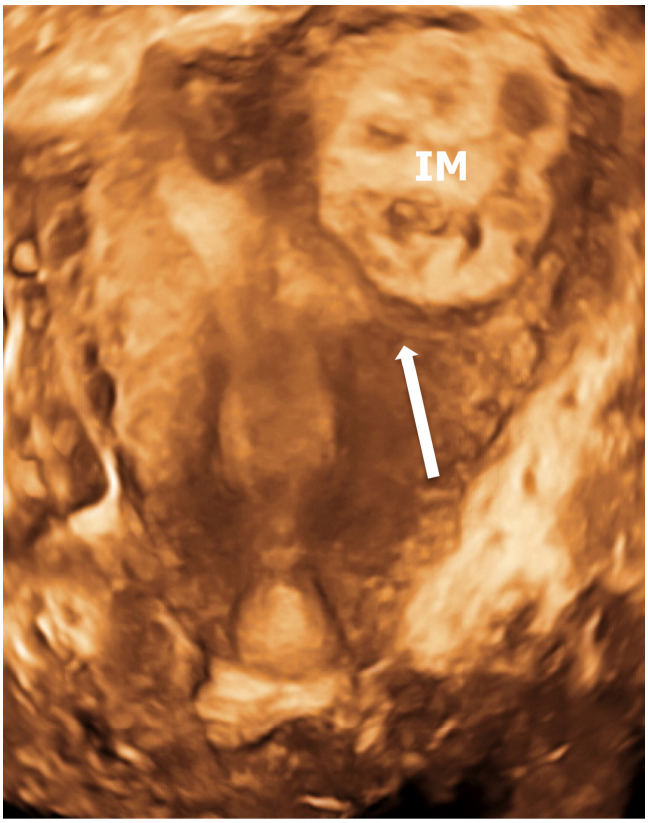

Figure 10 Three-dimensional coronal section of uterus showing complete intramural pregnancy (IM) implanted above left interstitial tube and elongating the tube (arrow).

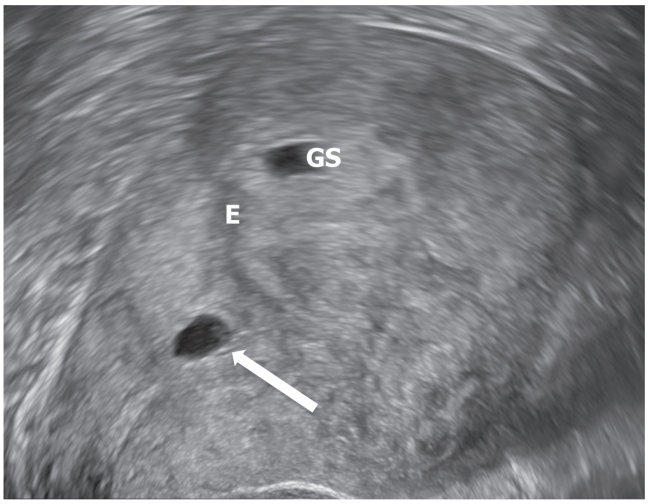

Figure 11 Longitudinal section of uterus showing gestational sac (GS) sited normally in endometrial cavity (E) and adenomyotic cyst (arrow) creating false impression of second pregnancy within the myometrium.

Complete intramural pregnancy without a gestational sac may be difficult to differentiate from GTD, such as in cases of persistent trophoblastic disease, choriocarcinoma or placental site trophoblastic tumor, as both may demonstrate increased vascularity on Doppler examination. However, hCG levels tend to be much higher in GTD, which could help in reaching the correct diagnosis.

Treatment

This series shows that there is no single standard treatment algorithm for patients presenting with an intramural pregnancy. Management depends on the severity of clinical symptoms, the location and depth of the pregnancy, the potential for viability and the woman's desire to preserve reproductive capability. If the pregnancy is deemed potentially viable, management decisions are made based on the perceived risk of morbidity to both patient and fetus.

A partial intramural pregnancy may progress to term and result in delivery of a healthy baby, but women should be counseled about the risk of abnormally adherent placenta, which is often complicated by heavy bleeding necessitating emergency life-saving hysterectomy. Although it is impossible to quantify this risk, one could extrapolate from the natural history of partial Cesarean scar ectopic pregnancy, which shares similar etiology[21–23].

In general, we have found that conservative management is the preferred option for complete intramural pregnancy. Conservative treatment of any ectopic pregnancy may involve systemic or local administration of methotrexate. We tend to use local injection, which is more effective in live pregnancies and requires a much lower dose of medication, thereby reducing the risk of systemic side effects. This approach was endorsed in the recent guideline on the management of Cesarean scar ectopic pregnancy by the Society for Maternal-Fetal Medicine, which advises against using systemic methotrexate for conservative management[24].

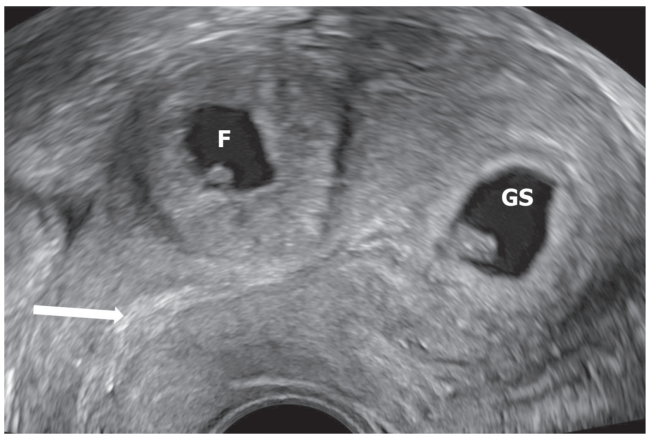

Figure 12 Longitudinal section of uterus showing normally sited gestational sac (GS) containing embryo, and degenerating cystic fibroid in posterior uterine wall (F), mimicking intramural pregnancy. Arrow indicates cervical canal. Image curtesy of Ms Catriona Stalder, Queen Charlotte's & Chelsea Hospital, London, UK.

The size of the pregnancy generally gives an indication of the time that it may take for the pregnancy to resolve and the importance of the commitment of a woman to comply with follow-up. Surgical management may be indicated if conservative management is either unsuccessful or unacceptable to the patient. A laparoscopic or open transabdominal excision with hysterotomy and repair is required to excise a complete intramural pregnancy, but this was not required in any of our patients. This procedure can be associated with an increased risk of uterine rupture in future pregnancies. Women should be informed that there is no strong evidence regarding the optimal time interval between the surgery and a future pregnancy. However, as for myomectomy, most clinicians advise a delay of 3–12 months to allow sufficient time for the uterus to heal[25].

For treatment of partial intramural pregnancy, transcervical suction evacuation is usually feasible and is the treatment of choice. This approach is similar to surgical treatment of Cesarean scar ectopic pregnancy, which has been described previously[26]. The procedures should be performed under transabdominal or transrectal ultrasound guidance to minimize the risk of uterine perforation and incomplete evacuation of pregnancy. In cases of larger and/or vascular pregnancy embedded deep into the myometrium (Figure 4), additional hemostatic measures, such as insertion of a cervical suture or Foley balloon or UAE, may be necessary.

Conclusions

Intramural pregnancy is a rare condition, which is difficult both to diagnose and to manage. In our series of 18 patients, seen over a period of 14 years, only 50% were diagnosed correctly at the initial visit, despite the study taking place in a tertiary center. It is therefore likely that intramural pregnancies are under-recognized and under-reported. It is not clear whether other diagnostic modalities, such as MRI, could help with earlier detection, as they are usually employed in clinical practice only when ultrasound findings are inconclusive. Assessing the depth of myometrial involvement is critical for planning of management, as partial intramural pregnancies are usually amenable to surgical evacuation, whilst conservative management is more appropriate for those which are confined to the myometrium. Our findings suggest that both conservative and surgical treatment of first-trimester intramural pregnancy tends to be successful, with preservation of reproductive function in most women.

Determination of the exact location of the pregnancy and successful surgical evacuation requires a high level of gynecological ultrasound skill and, ideally, patients with suspected intramural pregnancy should be referred to a specialist tertiary-level unit with expertise in managing rare types of ectopic pregnancy. We propose that an international registry is developed for intramural pregnancy, as this will allow collection of anonymized data on diagnosis, natural history and management of this rare form of uterine ectopic pregnancy. Data from this registry could facilitate the running of prospective, multicenter studies on the diagnosis and treatment of intramural pregnancy using standardized core sonographic diagnostic criteria to ensure high-quality research.

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