



Intramural ectopic pregnancy: An individual patient data systematic review

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ABSTRACT

Intramural pregnancies (IMP) are very rare and represent about 1% of ectopic pregnancies (EPs). Despite a few reported cases, there is limited awareness & knowledge among sonographers and physicians. Moreover, no established diagnostic or treatment protocol exists for such a condition. This study identifies and synthesizes what is known about IMP, including etiology and pathophysiology, common clinical presentations, imaging features, laparoscopic and hysteroscopic findings, and management. PUBMED and Google Scholar were queried to identify eligible studies. All articles on IMP in human subjects available in English and French languages were included. Other types of ectopic pregnancies, including cesarean scar and cervical ectopic pregnancies, were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and a narrative synthesis approach were used to systematically review the medical literature. 82 cases distributed around 27 countries with an average maternal age of 32.07 years and gestational age of 9.27 weeks were eventually selected for this study. History of curettage was the most common risk factor reported in 30 (36.58%) patients, followed by history of salpingectomy, assisted reproduction with embryo transfer, and previous cesarean delivery, in 10(12.19%), 10(12.19%), and 9(10.97%) patients respectively. Ultrasound was performed in 80(97.56%) cases. Of the 66 reported ultrasound findings, 29 were diagnostic or suggestive of IMP. MRI, laparoscopy (both diagnostic & surgical) and diagnostic hysteroscopy were carried out on 18(21.95%), 36(43.9%) and 22(26.83%) patients respectively. Histopathologic examination mainly performed after surgery was the gold standard for confirming the diagnosis. Management involved conservative (3.65%) approach, medical treatment with methotrexate or potassium chloride (23.17%), and surgical interventions. The latter includes laparoscopic surgery (25.61%), laparotomic surgery (23.17%), and hysterectomy (13.41%). IMP is a rare but potentially lethal clinical entity. A significant proportion of patients are asymptomatic and have no known risk factors. Correlation between clinical history and imaging findings is vital to establish a prompt diagnosis and reduce the risk of a catastrophic outcome.

1. Introduction

An ectopic pregnancy (EP) is a developing gestation outside the uterus, most commonly in the fallopian tubes. Intramural pregnancy (IMP) refers to a very uncommon EP located within the uterine wall, partially or completely surrounded by myometrium, and separate from the uterine cavity and fallopian tubes or the round ligaments. The trophoblast invades beyond the endometrial-myometrial junction, with the gestational sac (GS) partially or completely implanted within the uterine myometrium. It is the rarest type of EP [1], and accounts for approximately 1% of all EPs [2]. It was first reported by Theodore Doderlein in 1913 on a woman with adenomyosis. IMPs can easily be

misdiagnosed, especially at an advanced gestational age (GA), when the endometrial lining/cavity becomes effaced. There are various hypotheses about its etiology and pathophysiology, including the creation of a false tract secondary to trauma to the endometrial cavity. Nonetheless, IMP cases without prior uterine trauma or surgery have been reported. Urgent recognition and management of IMP is vital, as delayed diagnosis can result in rupture with life-threatening hemorrhage. The mortality rate is nearly 2.5% [3]. There have only been a few reported cases or small series of IMPs in the literature. However, there is still limited awareness and knowledge among sonographers and interpreting physicians (radiologists, obstetricians, gynecologists, emergency physicians). Furthermore, no established clinical practice guidelines exist to

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direct diagnosis, management and follow-up. We reviewed individual case reports on IMP and summarized the clinical and imaging features as well as management strategies for this rare and potentially devastating obstetric condition.

2. Objective

The objective of this individual patient data systematic review was to identify and synthesize what is known about IMPs, including etiology and pathophysiology, common clinical presentations, imaging features, laparoscopic and hysteroscopic findings, and management.

3. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [4] guidelines were used to conduct a systematic review of the medical literature.

3.1. Eligibility criteria

We selected cases of IMP published in peer-reviewed, PUBMED-indexed, and Google Scholar journals. All articles on IMP in human subjects available in English and French languages were included. As described by Memtsa and colleagues [1] and Auer-Schmidt and colleagues [5], we defined IMP as a unique clinical entity with clinicopathologic features distinct from those of cesarean scar and cervical EPs. Cases of cesarean scar and cervical EPs were therefore excluded. Case reports of EP outside the uterus were also excluded.

3.2. Information sources

In April 2022, we performed a comprehensive search of the PUBMED database. The following terms were used and relevant citations assessed: “intramural pregnancy,” “intramural ectopic pregnancy,” and “intra-myometrial pregnancy.” The terms “human” and “case report” were used as filters. A total of 65 articles published between 1965 and 2021 were selected. Google Scholar was also queried using the same terms and yielded an additional 36 articles.

3.3. Selection process

All citations identified were selected for abstract review. Articles not related to IMP or published in languages other than English or French were excluded. The remaining publications were selected for a preliminary evaluation during which incomplete and out-of-print articles were excluded. We then proceeded to the full-text evaluation and those considered relevant were included for final review. The initial review of abstracts was carried out independently by two individuals. During the final review, relevant data were extracted from case descriptions. Those include the first author’s name, country & year of publication, maternal & gestational ages, mode of conception, clinical presentation, obstetrics & gynecologic history, preliminary ultrasound diagnosis, ultrasound, MRI, CT, hysteroscopy & laparoscopy findings, and management (Table 1).

4. Results

A total of 65 and 36 articles were selected from the PUBMED and Google Scholar indices, respectively, for a total of 101 articles (including nine case series). After removing a duplicate study, twelve additional studies were excluded after abstract review, as the findings were unrelated to IMP. Six articles were written in languages other than French and English. Ten additional articles were excluded because they were either incomplete or the full text was out of print. 72 articles comprising 87 individual case reports were reviewed in detail. Five did not meet the inclusion criteria. A total of 82 case studies (patients) were included in

the review (Fig. 1).

Patients’ ages ranged from 19 to 44 years (mean 32.07 years, SD \pm 5.67 years) and the reported GA ranged from 4 weeks to 37 weeks [mean 9.27 weeks, SD \pm 5.68 weeks]. A total of 11 patients (13.41%) conceived through assisted reproduction, 10 of which involved embryo transfer. A history of spontaneous and/or induced abortion was reported in 37 patients (45.12%). With the exception of two, all the remaining patients included in the analysis had at least one risk factor for IMP.

History of curettage was the most common risk factor, reported in 30 (36.58%) patients, followed by history of salpingectomy in 10 patients (12.19%), assisted reproduction techniques with embryo transfer (ART-ET) in 10 patients (12.19%), and previous cesarean delivery in 9 patients (10.97%) [Fig. 2].

IMP rupture necessitating emergency laparotomy was reported in 12 patients (14.63%). GA at the time of rupture ranged between 5 weeks, 6 days and 26 weeks, 0 days (mean: 15.11 weeks, SD \pm 6.18 weeks). Clinical presentations and complications are summarized in Fig. 3.

The diagnosis of IMP was confirmed on pathology [22 cases (26.83%)], Magnetic Resonance Imaging (MRI) [14 cases (17.07%)], exploratory laparotomy [12 cases (14.63%)], and diagnostic laparoscopy [10 cases (12.19%)] (Fig. 4). The proposed diagnostic steps are presented in Fig. 5.

A presumptive diagnosis of IMP was established by sonography in 29 cases, though ultrasound findings were not reported in 16 cases (19.51%). Among cases in which ultrasound findings were included, 13 (19.7%) were wrongly diagnosed as either angular, cornual, or interstitial pregnancy (Fig. 6) and eventually proven to be IMP.

Management of IMP involved laparoscopic (21 cases [25.61%]) or laparotomic (19 cases [23.17%]) resection of the pregnancy mass followed by surgical repair. Hysterectomy and medical therapy were performed in 11(13.41%) and 19(23.17%) patients respectively. Only 3 (3.65%) patients had a successful conservative approach with the IMP resolving without an intervention (Fig. 7).

Various imaging modalities were used to evaluate suspected IMP. Ultrasound was performed in the vast majority (80 patients [97.56%]). MRI and Computed Tomography (CT) scan were used less frequently (18 cases [21.95%] and 4 cases [4.88%], respectively). Laparoscopy (diagnostic and surgical) and diagnostic hysteroscopy were performed in 36 patients (43.9%) and 22(26.83%) respectively. The only two cases in which ultrasound wasn’t performed were reported in 1965 by McGowan [24], when diagnostic ultrasound wasn’t widely available in clinical practice.

5. Discussion

To the best of our knowledge, this is the largest and most comprehensive review of IMP to date, including a total of 82 cases across 27 countries (Table 1).

5.1. Pathogenesis and risk factors

The etiology and pathophysiology of IMP remain to be definitively established. It has been postulated that IMP results from increased lytic activity of syncytiotrophoblasts with resultant defective decidualization, which allows the conceptus to penetrate the myometrium or implant in the serosa following external migration [2,30,39]. Auer-Schmidt and colleagues [5] described three contributory factors that may lead to IMP. First is a false tract between the endometrium and the myometrium, most often secondary to prior uterine/endometrial trauma during instrumentation or surgery. The second is in vitro-fertilization with embryo transfer (IVF-ET), during which embryos are mistakenly placed into the myometrium through the false tract. The third factor is adenomyosis, which enhances myometrial receptivity thereby increasing the likelihood of myometrial implantation. Other authors suggest that intrauterine trauma during difficult embryo transfer results in a false passage [2,71,74].

Table 1
Detailed characteristics of included studies [1–3,5–73].

Case	First Author	Year of Publication	Country of study	Maternal Age/Mode of conception	Clinical presentation	Gynecologic/Obstetric history	USS findings	Preliminary ultrasound diagnosis	MRI findings	Hysteroscopy findings	Laparoscopic findings	Diagnostic confirmation	Management
1	Auer-Schmidt MM [5]	2021	Germany	40/IVF-ET	Asymptomatic	G2P0A1; Adenomyosis, previous curettage, hysteroscopic adhesiolysis	Gestational sac (GS) + Yolk Sac (YS) + Fetal pole (FP) without fetal heart rate (FHR) in the myometrium of the posterior uterine wall & an empty uterus.	IMP		empty uterus with visualization of Fallopian tubes (FTs) ostia, and a false tract visualized extending for 6.5cm from the external cervical os with the conceptus implanted in the upper.		TVS	Hysteroscopic mechanical curettage of the GS
2	Liu Y [6]	2020	China	28/ IVF-ET	Asymptomatic	G2P1A0, Previous Salpingectomy	1. Empty endometrial cavity; 2. No fetal pole or Yolk Sac; 3. Ill-defined hypoechoic structure without Gestational Sac nor fetal pulsation apparently between the right ovary & the uterus.	Right interstitial or Cornual pregnancy		No sign of a gestation sac. Slight intrauterine adhesion in the fundus & some decidua tissue hyperplasia. Visible ostia bilaterally	exploratory Laparoscopy (mass in the myometrium & protruding to the right side/horn)	exploratory Laparoscopy + Pathology report	Laparoscopic surgical excision
3	Chaikof M [7]	2020	Canada	35/spontaneous	Abd bloating & discomfort	G3P2A0, Previous curettage and Intrauterine adhesions	1. Uterine intramural pregnancy; 2. Gestational Sac located within 3mm of the uterine serosa & outside the endometrial cavity	Intramural pregnancy				Gross Pathology	Laparotomy with fundal hysterotomy & removal of ectopic pregnancy
4	Zhang Q [8]	2019	China	30/spontaneous	vaginal bleeding	G1P1A0; Previous Cesarean section (C/S)	1. Echogenic structure in the posterior myometrium (1 X 0.8cm), near the fundus; 2. Endometrial cavity not connected to the sac; 3. Intramyometrial arcuate vasculature on Doppler; 4. Serosal surface of the mass had feeble myometrial tissues. 5. Power Doppler displayed trophoblastic peripheral blood flow	Interstitial pregnancy			A bulging mass in the posterior wall below the left uterine horn with a purplish-blue colored surface with posterior serosal layer adhered to the surrounding intestines	Emergency laparoscopy	Laparoscopic guided incision & removal of the sac following by local methotrexate (MTX) injection to kill the remaining trophoblastic tissues
5	Liu NN [9]	2017	China	34/ spontaneous	Nausea (Asymptomatic)	G1P1A0; Adenomyosis, previous laparoscopic surgery for endometriosis treatment	1. Heterogeneous mass (3.7 x 3.3cm) in the posterior wall & extending to the serosa. 2. Color Doppler: abundant flow	Intramural pregnancy	An irregular signal area in the left wall within the myometrium of the uterus, surrounded by multiple visible tortuous low signal flow-void vascular shadows	Empty uterus	1. Mass protruding out of the left uterine wall; 2. Extremely thin serosal layer covering the mass	Pathology report	Laparoscopic surgical excision
6	Liu NN [9]	2017	China	19/ spontaneous	Irregular vaginal bleeding	G1P0A0; Previous curettage	1. Heterogeneous mass in the posterior uterine wall; 2. Color Doppler: Abnormal Increase in blood flow signals	Intramural pregnancy			Bulging mass in the left posterior uterine wall	Pathology report	Laparoscopic surgical excision
7	Liu NN [9]	2017	China	40/ spontaneous	Severe abdominal pain	G4P0	1. Heterogeneous echogenic mass in the right side of the uterine wall, close to cornual tissues; 2. No connection to the endometria; 3. positive embryo and heart Beat	Intramural pregnancy		No gestational sac	Protruding cornual tissues with intact cornua	Pathology report	Laparoscopic surgical excision
8	Bannon K [10]	2013	USA	27/ spontaneous	Asymptomatic	G1P0A0; Previous Myomectomy	Description of displayed image 1. Empty endometrial cavity; 2. Fundal Gestational Sac + thin myometrium posteriorly, peripheral vascular flow around the sac	Missed Abortion	CT findings: Empty cavity, 2. posterior left fundal intramural pregnancy			3D ultrasound and CT scan	Systemic methotrexate (MTX) following B-HCG monitoring. Then Da Vinci Laparoscopic procedure to remove the persistent mass
9	Memtsa M [1]	2013	UK	38/ spontaneous	Heavy vaginal bleeding	G5P3A1; previous curettage	Retained products in the left posterior uterine myometrium	Incomplete Miscarriage				USS	Conservative management with follow up of B-HCG level
10	Memtsa M [1]	2013	UK	33/ spontaneous	Post-partum bleeding + 5 weeks	G1P1A0	Retained products measuring 1.5 cm with pregnancy tissues extending beyond the myometrial junction, partially embedded to the myometrium of the posterior uterine wall					USS	Dilation & curettage
11	Memtsa M [1]	2013	UK	38/ spontaneous	vaginal bleeding; abdominal pain		3mm focus of hyperechoic tissue detected deep in the post uterine wall. Highly vascular on Doppler exam.	Intramural pregnancy				USS- guided biopsy	Local Methotrexate injection
12	Bouzar Z [11]	2010	Iran	28/ spontaneous	1. Acute abdomen; 2. Hypovolemic shock (Ruptured at 26 weeks)	G3P0A2; Previous Curettage(twice) and myomectomy	free abdominal fluid, non-viable fetus in the abdominal cavity	Intrauterine pregnancy				exploratory laparotomy	Exploratory laparotomy with myometrial repair
13	Bouzar Z [11]	2010	Iran	32/ spontaneous	abdominal pain + vaginal bleeding	G2P0A1; Previous curettage	At 6 weeks: Thickened and mildly homogeneous endometrium; no Gestational Sac in the endometrial cavity; Moderately heterogeneous pattern noted in the posterior myometrium; Color Doppler: Moderate to gross hypervascularity in the area. At 8 weeks: Two Gestational Sacs in the posterior myometrium	Intramural twin pregnancy				MRI	Intramuscular methotrexate followed by B-HCG level monitoring
14	Cohen J [12]	2016	France	38/ spontaneous	vaginal bleeding + abdominal pain	Previous abortion via dilatation & curettage	1. Empty Uterus; 2. circular hyperechoic area with high peripheral vascularization localized within the posterior uterine wall.		abnormal area/mass localized within the posterior uterine wall displaying a T1 hypointense and T2 hyperintense.			MRI	Intramuscular methotrexate followed by B-HCG level. No significant improvement, then suction aspiration of the IMP and local methotrexate injection
15	Verghese T [13]	2012	UK	27/ spontaneous	vaginal bleeding	G3P1A1	1. Irregular pregnancy (non-viable Fetal Pole) located near the cornua	Missed Abortion		Empty uterus	Asymmetrically enlarged uterus with swollen fundus, small hemoperitoneum	MRI	Intramuscular methotrexate, then monitoring B-HCG level
16	Lee GS [14]	2003	Korea	25/ spontaneous	Asymptomatic	History of right adnexectomy	1. Gestational Sac + Fetal pole +Yolk sac separated from the endometrium. 2. 3D Ultrasound showed a live embryo in a Gestational sac surrounded by myometrium below the Right cornu, outside the endometrium					Laparotomy	Laparotomy with excision of the conceptus
17	Jin H [15]	2004	China	29/ spontaneous	low abdominal pain + vaginal bleeding	G3P1	Ill-defined mass in the fundal myometrium adjacent to the covering of the uterus					Laparotomy	Laparotomy with excision of the mass
18	Jin H [15]	2004	China	39/ spontaneous	Irregular vaginal bleeding	G4P1	Amorphous echoes in the ut cavity	Incomplete abortion	CT findings: Trophoblastic tumor with deep invasion in the myometrium			Pathology	Sub radical abdominal hysterectomy (suspected intramural choriocarcinoma, proven to be IMP on biopsy)

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Table 1 (continued)

19	Wu PJ [16]	2012	Taiwan	20/ spontaneous	Dull lower abdominal pain	G3P0A2; Previous curettage(twice)	ill-defined fundal mass without FF adjacent to the right cornu. Color Doppler: high blood flow at the periphery of the mass & difficult to differentiate the boundary from the myometrium and endometrial cavity	Aneembryonic right cornual or Invasive molar pregnancy		Empty uterus; 2. Endometrial thickening; 3. visible ostia	Unruptured hypervascularized mass protruding from the right fundal myometrium & distinct from fallopian tubes	Pathology	Laparoscopic surgical excision + Intramuscular methotrexate
20	de Tové KM [17]	2015	Benin republic	32/ spontaneous	Lower Abdominal pain+ abnormal vaginal bleed	G1P0A1; Previous curettage	1. Gestational Sac with double trophoblastic ring; 2. Visible endometrium without decidual reaction; 3. Distortion of Uterine contour; 4. Thinning of the myometrium related to the Gestational Sac					Surgery(hysterectomy)	Hysterectomy
21	Hlinceká Krasňna [18]	2002	Czech Republic	35/ spontaneous	Lower Abdominal Pain (Right iliac fossa pain)	Previous C/S; transservic hysteroscopic resection of retained products of conception (RPOC)	Intramural ectopic pregnancy	IMP				laparoscopic surgery	Laparoscopic surgical excision
22	Bernstein HB [19]	2001	USA	35/ spontaneous	Left lower Quadrant pain	G3P0A2; previous curettage	Gestational Sac + Yolk sac distinct from the endometrial cavity. Both endometrium & Gestational Sac appear surrounded by myometrium	Ectopic pregnancy			2cm bulging mass on the left side of the uterus, located 1 cm below the cornu; 2. Mass covered by serosa and appearing to be in the myometrium	Diagnostic Laparoscopy	Expectant: gradual regression of the mass, eventual disappearance
23	Wang J [20]	2013	China	20/ spontaneous	Vaginal bleeding	G2P0A1; Previous curettage	1. Empty endometrial cavity; 2. Gestational Sac in the Left posterior myometrium + with a sinus connecting the sac to the endometrial cavity. 3. Color Doppler: Abundant vascularity with a resistive index of 0.55. 4. 3D Ultrasound: Gestational sac in the left posterior uterine myometrium 1.4 cm above the os and clearly out of the endometrium.	Interstitial pregnancy		Bilateral tubal ostia without dilatation. No septum in the uterine cavity, a dimple in the left internal uterine wall		3D TVS	Hysteroscopic excision of the gestational sac with systemic methotrexate
24	Glass T [21]	2010	USA	29/ spontaneous	vaginal spotting	G1	1. Gestational sac + no fetal pole; 2. Highly vascular tissues around the Gestational sac, with difficult differentiating myometrium from the vascular tissues	Molar pregnancy	Complex heterogeneous mass involving the uterine myometrium, extending to the fundus, empty endometrial cavity separated from the mass		Large 6 x 5cm mass located in the posterior fundal portion of the uterus, distant from the cornual region with active bleeding from the site of Rupture	MRI + diagnostic Laparoscopy	Initially: Suction curettage (yielded nothing); then Laparotomy with surgical excision
25	Liu Y [5]	2014	China	38/ spontaneous	intermittent vaginal bleeding	G1P1A0; History of Intrauterine device (IUD) use	Color Doppler: Uneven echoes in muscle layers & sufficient blood flow signal in the enlarged area of the uterus	Leiomyoma with Adenomyosis				Pathology	Laparoscopic subtotal hysterectomy
26	Qng C [2]	2010	Singapore	36/ spontaneous	vaginal spotting	Adenomyosis	1. Gestational sac in the posterior myometrium, 2. Coarse posterior myometrium	Intramural pregnancy				USS	Uss-guided local Potassium Chloride (KCl) & methotrexate injection
27	Katano K [22]	1999	Japan	33/ spontaneous	Asymptomatic	Previous curettage for molar pregnancy	1. Non-Visible fetal pole + septum thickening of 6mm between the Gestational sac & the endometrium	Missed Abortion				MRI	TVS USS-guided methotrexate local injection
28	Ashraf M [23]	2003	USA	36/ IVF-ET	NP	NP	Eccentric Gestational Sac with thinning of the myometrial mantle & visualization of the endometrial stripe distinctly from separate from the Gestational Sac. Sac surrounded by myometrium in all directions			IMP medial to the round ligament		Diagnostic Laparoscopy + USS	Systemic methotrexate which failed. Then mini-laparotomy with IMP nucleation followed by suction curettage
29	Lu HF [24]	1997	Taiwan	37/ spontaneous	Intermittent vaginal bleeding	G4P1A2; Adenomyosis; previous C/S and curettage (twice)	Asymmetrically enlarged uterus + ill-defined mass 5.3 x 3.3cm within the thickened post myometrium. Another 3.8 x 1.4 x 2.0cm echoluculent cyst noted with diffused blood flow at the periphery of the cyst on Color Doppler	Intramural pregnancy				Laparotomy	Laparotomy with excision of the mass
30	Chida H [3]	2016	Japan	31/ spontaneous	NP	Previous cervical conization and curettage	Gestational Sac + live Fetus; Color Doppler: hypervascularity around the sac, which was located within the fundal wall	Intramural pregnancy	Gestational sac growing into the fundic uterine wall			MRI	Uterine artery embolization (UAE), followed by laparotomy with resection of the lesion 3 days later
31	Ko HS [25]	2006	S Korea	30/ spontaneous	Vaginal bleeding	G4P1A3; previous C/S and curettage (3 times)	Round mass of mixed echogenicity in the previous cesarean scar area		A multilobulated mass in the lower anterior uterine wall with irregular heterogeneous signal intensities on T2-weighted & enhancing papillary solid components with a non-enhancing necrotic portion after gadolinium infusion			MRI	Intramuscular methotrexate with leucovorin
32	Ko HS [25]	2006	S Korea	28/ spontaneous	NP	G6P0A6; six previous curettages	Echogenic mass in the posterior uterine wall. 2. Color Doppler: significant internal blood flow		Ovoid mass on T2-weighted in the posterior uterine wall that had multiple tortuous tubular structures of high signal intensities & a fine communicating tract with the endometrium. After gadolinium infusion, these lesions enhanced as much as the uterus.			MRI	Intramuscular methotrexate with leucovorin
33	Lyu J [26]	2018	China	26/ IVF-ET (frozen)	Asymptomatic	History of salpingectomy	Mass in the cornu separate from the uterine cavity & surrounded by uterine musculature				No bulging at the surface of the uterus	Pathology	Laparoscopic enucleation of the IMP
34	YeKuang [27]	2013	China	34/ spontaneous	Lower abdominal pain	G2P1A0; Adenomyosis; previous laparoscopic surgery for endometriosis	Less uniform myometrial echoes & heterogeneous echogenic area stretching the serosal layer of the posterior uterine wall; 2. Color Doppler: high blood flow	Intrauterine pregnancy		Empty uterus, thickened endometrium containing blue pigmented cysts	A bulging mass with an extremely thin serosa arising from the left side of the posterior uterine wall	Diagnostic Laparoscopy	Laparoscopic resection

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Table 1 (continued)

35	Doulias V [28]	2003	Greece	31/ spontaneous	Menorrhagia x 5 months	G3P1A2; two previous curettages	"Intramural myoma"	Intramural Myoma			Pathology	Excision of the mass (nonspecific)
36	Wang S [29]	2013	China	28/ spontaneous	Lower abdominal pain	G2P0A1; Previous curettage	Gestational sac + Yolk sac distinct from the endometrial cavity	Intramural pregnancy	Gestational sac seemed surrounded by the myometrium at uterine fundus.		MRI	Bilateral Uterine artery embolization (LAE)
37	Hamilton CI [30]	1992	Saudi Arabia	25/ IVF-ET	Abdominal pain + signs of hemorrhagic shock (Ruptured at 20 weeks)	G2P0A0; Previous bilateral salpingectomies	Intact pregnancy located quite far Right in the uterus but within the outline of the uterus. Endometrial cavity visible to the left of the pregnancy sac in transverse plane.				Laparotomy	Laparotomy with uterine repair
38	Park WI [31]	2006	S Korea	35/ IVF-ET	painless vaginal bleeding	History of laparoscopic myomectomy	Gestational sac-like structure situated within the subserosal region of the posterior uterine wall, completely separated from the endometrial cavity, as the gestational grew, serosal surface lacked any visible myometrial tissue.	Intramural pregnancy		Left Posterior uterine wall protrusion with increased vascularity. In the center of the bulge, the fluid in the gestational sac was visible through a thin layer of serosal coverage.	Laparoscopy	Laparoscopic incision & enucleation
39	Tucker SW [32]	1995	USA	36/ spontaneous	Asymptomatic	G5P2A3	Viable Intrauterine pregnancy (IUP)	Intrauterine pregnancy + Numerous myomas	Empty uterine cavity with some necrotic debris. Bilateral ova were normal		Laparoscopy + Pathology	Laparoscopic resection
40	Kirk E [33]	2013	UK	25/ spontaneous	Lower abdominal pain (Ruptured at 5 weeks 6 days)	G4P1A2; previous C/S and curettage	Empty uterus; Right adnexal mass close to the cornu, & containing a Gestational sac.	Right tubal Pregnancy		2 x 2 x 2 cm ectopic pregnancy which ruptured through the post uterine wall, with normal Fallopian tubes	Pathology	Laparotomy with resection of the ectopic pregnancy
41	Petit L [34]	2012	France	36/ spontaneous	Asymptomatic	Not Provided	Normal fetus, no evidence of eccentric placental implantation.	Intrauterine pregnancy			Pathology	Laparotomy followed by cesarean section (C/S); Then hysterectomy owing to excessive bleeding (Intramural placental)
42	Ginsburg KA [35]	1989	USA	33/ spontaneous	abdominal pain+ unstable vitals (Ruptured at 16 weeks)	G9P2A5; Five previous curettages.	Gestational sac with fetus outside the Uterus with intra-abdominal free fluid	Right Cornual Pregnancy (Ruptured)			Pathology	Laparotomy with total abdominal hysterectomy (TAH)
43	Karakök M [36]	2002	Turkey	41/ spontaneous	Left-sided Lower abdominal pain	G6P4A2	Gestational sac without Fetal Pole				Pathology	Explorative laparotomy + Left cornual resection
44	Mailek Mellouli M [37]	2013	Tunisia	35/ spontaneous	NP	G3P2A0; Previous salpingectomy	Gestational sac containing a 13 week-embryo distinct from the endometrial cavity with intra-abdominal fluid. The gestational sac appears surrounded by myometrium.	Cornual Pregnancy		Left 8 cm bulging adnexal mass from the left side of the uterus, covered by serosa revealing the gestational sac (GS) and seemed embedded in the myometrium.	Diagnostic Laparoscopy	Laparotomy with enucleation of the IMP
45	Liu D [38]	2019	China	34/ spontaneous	Asymptomatic	Previous C/S and myomectomy	TVS: bulging gestational sac located in the left cornual area. C Doppler: abundant blood flow between the Gestational sac & Left cornual area.	Cornual Pregnancy	Empty uterus, empty Fallopian tube Ostia. A violet blue appearance in the area about 1.5cm inferior to the left Fallopian tube ostium.		Contrast-enhanced USS	Laparoscopic excision
46	Khalifa Y [39]	1994	UK	31/ spontaneous	Lower abdominal pain + brown vaginal discharge	Previous traumatic hysterectomy	Viable singleton pregnancy in the posterior uterine wall, completely separated from the endometrial cavity by a distance of about 7mm.	IMP			TVS	USS-guided Potassium Chloride (KCl) Local injection
47	Cava EF [40]	1978	USA	29/ spontaneous	epigastric pain + Lower abdominal pain (Ruptured at 21 weeks)	G3P2	viable gestation at 21 weeks	Partial abruptio placenta			Pathology	Laparotomy with total abdominal hysterectomy (TAH)
48	Lone FW [41]	2001	Pakistan	40/ spontaneous	Metrorrhagia	GBP7A1; Previous curettage	Hypoechoic area within the myometrium, suggestive of fibroid close to the left cornu with evidence of central necrosis	Leiomyoma			Pathology	total abdominal hysterectomy (TAH)
49	Meghna Barmase [42]	2020	India	32/ spontaneous	vaginal bleeding	G3P1A1; Previous C/S and curettage	Empty uterus, heterogeneous hypoechoic intramural space occupying lesion (SOL) noted mid posterolaterally, embedded in the myometrium, away from the uterine cavity with no communication with the endometrial lining. Color Doppler: Florid intraliesional and peripheral vascularity noted seen within the mass with high velocity & low resistance waveform.	IMP		Focal bulge posterolaterally, surrounded by myometrium; 2. Localized increased in vascularity noted in the serosal surface of the bulge.	Diagnostic Laparoscopy	Dilation & curettage which yielded nothing; Then Systemic methotrexate
50	Song QY [43]	2004	China	44/ spontaneous	NP	G6P2A4; previous C/S and curettage	Distinguishable distal endometrium with unclear middle & upper endometria. 2. Heterogenous hyperechoic mass with clear boundaries in the upper middle uterine segment. Several irregular liquid dark areas in the mass.	Trophoblastic tumor	CT scan: cystic & solid space-occupying Lesions (SOLs) in the uterine cavity with unclear heterogeneous enhancement in the right uterine wall & fundus, reaching deep into the musculature. Low intensity foci in the anterior & posterior uterine walls, & one in the anterior wall reached the serosa		Pathology	diagnostic chemotherapy with (Etoposide+Methotrexate+Actinomycin D+cyclophosphamide); followed by hysterectomy, then hysterectomy
51	Nees J [44]	2020	Germany	24/ spontaneous	Asymptomatic	Previous miscarriage; History of C/S	Moderately developed endometrium, inconspicuous adnexa on both sides & no signs of free fluid. Mass didn't appear to communicate with the Fallopian tube (FT) or uterine cavity.	IMP			Surgery (laparotomy)	Laparotomy with excision of the IMP
52	Vaggs D [45]	2018	Australia	34/ spontaneous	Vaginal discharge + Right Iliac Fossa pain	P2A0; History of myomectomy	Live IMP + a thin layer of myometrium covering the pregnancy; Placental invasion also seen & thought to be over the site of previous myomectomy.	IMP	Gestational sac (8.0 x 7.9cm) containing mobile fetus within the myometrium of the right cornu, with marked thinning of the overlying myometrium to 3mm, with no hemoperitoneum		MRI	Initially local and Systemic methotrexate which failed; Then laparotomy with total abdominal hysterectomy (TAH)

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Table 1 (continued)

53	Kong L [46]	2017	China	20/ spontaneous	NP	G1P0A0; Previous curettage	Clear gestational sac (GS) with viable fetus and placenta previa; GS not connected to the endometrial cavity, with compressed myometrium between both of them.		Fetus with clear organs & compressed the lower segment. The gestational sac (GS) was not connected with the uterine cavity & endometrium, but embedded into the myometrium in the right posterior uterine wall. A linear hypointensity of the junctional zone was observed btw the GS & the uterine cavity on T2-weighted.		MRI	Laparotomy with excision of the IMP
54	Nabeshima [47]	2010	Japan	38/ spontaneous	NP	G3P1A0; Previous salpingectomy	Ill-defined gestational sac (GS) with fetal heart beat (FHB) within the fundal myometrium adjacent to the left cornu.	Cornual Pregnancy or IMP			Laparoscopic surgery	Laparoscopic surgical excision of the gestational sac
55	Moumna [48]	2020	Morocco	36/ spontaneous	Lower abdominal pain (eventually ruptured at 9 weeks)	G2P2A1	Gestational sac (GS) with live fetus; Empty endometrial cavity with both the endometrium & the GS appear to be surrounded by myometrium.	IMP			Laparoscopy + Pathology	Laparoscopic surgical resection followed by uterine repair
56	CALIRKAN [49]	2008	Turkey	21/ spontaneous	vaginal bleeding	G1P0A0	Gestational sac(GS) with yolk sac (YS) & fetal pole (FP), distinct from the endometrial cavity, surrounded by the myometrium. 3D-TVS: GS with a 2.0-0.4mm sinus tract connecting the endometrial cavity with the GS	IMP			3D TVS	Expectant management
57	Havutcu AE [50]	1999	UK	35/ ART	Right iliac Fossa pain + vaginal bleeding	Previous curettage	TVS: irregular gestational sac (GS) with no evidence of a yolk sac (YS). Repeat scan after 2 days showed a GS measuring 1.5 x 1.7cm found to the right of the uterine cavity.	Right cornual ectopic pregnancy		Asymmetric uterine fundus & very vascular right cornua	Laparotomy	Laparotomy with excision of the IMP
58	Yi Wang [51]	2015	China	21/ spontaneous	Persistent vaginal bleeding? retained products	G3P1A1	Ill-defined fundal mass near the Left fundus. Color Doppler: high blood flow at the periphery of the fundal mass. It was difficult to differentiate the boundary from the myometrium and the endometrial cavity	Left Cornual Ectopic Pregnancy; Invasive molar pregnancy	Empty uterus, endometrial thinness, bilateral visible ostia	protruding mass at the side of the uterine fundus & distinct from the fallopian tubes	Laparoscopy	Laparoscopic enucleation with uterine repair
59	Abdel-Gadir [52]	2009	UK	38/ ART-ET	NP	Previous miscarriage, bilateral salpingectomies & myomectomy	TVS: empty uterus, multiple lesions, non-homogenous myometrium in some areas; 3D-TVS: 2.75cm gestational sac (GS) medial and above the interstitial part of the Right tube with 7.6mm fetal pole	Cornual / interstitial pregnancy		Mass bulging out of the fundal area.	3D TVS & Laparoscopy	Laparoscopic incision & excision of the IMP
60	Qian Hu [53]	2021	China	35/ spontaneous	Irregular bleeding, 7 Retained products	G5P2A2; Previous abortion	Mixed echogenic mass embedded in the myometrium of the Right posterior uterine wall near the fundus. Color Doppler: High blood flow at the periphery of the mass such that it was difficult to distinguish the boundary between the myometrium & the endometrial cavity	IMP or Gestational trophoblastic tumor	CT SCAN showed a 2.5 x 2.5 cm abnormal mass within the right post uterine wall with an obscured boundary	Non-triangular endometrial cavity, bucket-shaped with non-visible right cornu. Most of the uterine wall covered by fibrous tissues. No intrauterine pregnancy (IUP), Fallopian tubes ostia not seen	Pathology	USS-guided laparoscopic incision followed by excision of the mass
61	W.D. Zou [54]	2019	China	32/ spontaneous	Status post dilation and curettage	G4P1A3; Previous transverse uterine adhesiolysis	Intrauterine Pregnancy (IUP)	Angular or IMP	Empty uterus, endometrial thinness, Visible ostia	Mass protruding from the fundal myometrium & distinct from the Fallopian tubes & ovaries	Laparoscopy(surgery)	Laparoscopic surgical incision & removal of the IMP
62	B. Bechev [55]	2017	Bulgaria	28/ WF-ET	Asymptomatic	G1P0A0; Previous partial salpingectomy	Enlarged and asymmetric uterus with an ectopic gestational sac(GS) with fetal pole in the posterior uterine wall. The GS completely surrounded by myometrium.	IMP		Round thickening of the posterior uterine wall, with size of 15mm	USS + laparoscopy	TVS-guided laparoscopic methotrexate gestational sac injection
63	McGowan L [56]	1965	USA	28/ spontaneous	Vertigo, abdominal pain, right shoulder pain, loss of consciousness, urinary & fecal incontinence (Ruptured at 15 weeks 2 days)	G1P0A0; Previous curettage		Ruptured tubal pregnancy.			Laparotomy	Laparotomy with total abdominal hysterectomy (TAH)
64	McGowan L [56]	1965	USA	24/ spontaneous	irregular bleeding, vague intermittent lower abdomen pain	G1P0A0; Previous curettage		Ectopic pregnancy or Ovarian cyst			laparotomy	Laparotomy with surgical resection
65	Zang L [57]	2021	China	33/ spontaneous	Vaginal bleeding, nausea, chest tightness	G4P1A2	A mass with uneven echoes & abundant blood flow in the right lateral wall of the uterus.	Gestational trophoblastic neoplasm		A projection surrounded by abundant tortuous vascularity	Pathology (histology & immunohistochemistry)	Chemotherapy (Etoposide+ Methotrexate + Actinomycin cyclophosphamide), followed by exploratory laparotomy
66	You SH [58]	2019	Taiwan	35/ spontaneous	Severe pelvic pain + hypotension (Ruptured at 9 weeks)	G5P3; Adenomyosis, previous Uterine arteries ligation for adenomyosis + IUD retrieval	Mass located in the uterus	IMP		Bulging gestational tissues with a rupture of the prior uterine scar with 1500ml hemoperitoneum	Laparoscopy + pathology	Laparoscopic surgical removal of the IMP with uterine repair
67	Yang B [59]	2020	China	31/ spontaneous	NP		Empty uterus with a gestational sac in the right horn of the uterus surrounded by myometrium.	IMP		Empty uterus gestational sac (GS) could not be assessed because deep inside the myometrium.	Laparoscopy	Laparoscopic incision & removal of the IMP
68	Fabian Kohls [60]	2016	Germany	28/ spontaneous	Vaginal bleeding	G2P0A1	Cystic structure in the posterior wall of the uterus. Color Doppler showed an area of 5.0 x 2.5cm with vascularization.	IMP		Uterine cavity of normal size & shape completely covered with decidua. No Intrauterine pregnancy or changes in the posterior wall of the uterus were seen.	Laparoscopy (diagnostic)	Laparoscopic incision followed by laparotomy + resection of the IMP
69	Su S [61]	2017	China	34/ spontaneous	Asymptomatic	G2P1A0; Adenomyosis	A heterogeneous mass measuring 4.9 x 4.8 cm in the left wall of the uterine	Gestational Trophoblastic disease		No Intrauterine pregnancy (IUP) & the left Fallopian	Laparotomy + pathology	Systemic methotrexate failed owing to severe reaction to the treatment; Then laparotomy with resection of the IMP

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Table 1 (continued)

							Fundus reaching the serosa, with several anechoic areas inside the mass demonstrating significant circumferential vascularity.			ostium was not easily delineated.				
70	Anis Fadhlouai [62]	2011	Tunisia	35/ spontaneous	Initially Asymptomatic; Then acute abdominal + hypovolemic shock (Ruptured at 13 weeks)	G5P1A2; Previous salpingectomy	A gestational sac (GS) with viable fetus near the right cornual region. The Endometrial cavity & GS are separated with no evidence of communication between them. The GS appears surrounded by myometrium.	IMP		A gestational sac with a fetus developing inside the fundic uterine wall. The placenta seemed to invade the myometrium.		Emergency Laparotomy	Laparotomy +with Removal of fetus & gestational sac followed by uterine repair	
71	Xie QJ [63]	2022	China	31/ IVF-ET	Asymptomatic	G3P0; Previous right salpingectomy and Hysterectomy for polypectomy & adhesiolysis	TVS: Heterogeneous echogenic area measuring 1.40 x 1.26 cm in size arising from the uterine fundus with a 0.48 cm x 0.37 cm anechoic region inside and surrounded by myometrium. Color Doppler: abundant blood flow. This region seemed to have a slender and extremely hypoechoic area stretching to the uterine cavity. In addition, a hypoechoic structure with an indistinct boundary measuring 2.74 x 1.61 cm in size was observed in the anterior myometrium near the uterine fundus, which was thought to be a uterine adenomyoma	IMP			bulging and unruptured mass measuring approximately 2 cm in the left side of the anterior uterus with a purplish-blue-colored surface distinct from the uterus & the Fallopian tubes.	Laparoscopy & pathology	Laparoscopic removal of the IMP followed by local methotrexate injection	
72	Yahaya UR [64]	2020	Nigeria	38/ spontaneous	Severe abdominal pain + Signs of Hemorrhagic shock (Ruptured at 16 weeks)	G3P2A0	Peritoneal fluid with a gestational sac (GS) containing a live fetus at 16 weeks. The endometrial echo complex seen below the GS					Laparotomy	Exploratory laparotomy with subtotal Hysterectomy	
73	Lazović B [65]	2010	Serbia	32/ spontaneous	Retained products suspected	G1P1A0	Hypercholesteric mass in the left uterine horn, enclosed by serosa & appeared to be in the myometrium	Trophoblastic Neoplasia	Same as in ultrasound		Carried out, but details not provided	Pathology	Intramuscular methotrexate, then laparoscopic surgery with excision of the mass	
74	Capogna MV [66]	2014	Italy	37/ spontaneous	Threatened miscarriage suspected	Previous Hysterectomy for Asherman's syndrome and two laparotomic myomectomies	3.3 x 2.0cm mass in the right Lateral uterine Fundus, with weakly hypercholesteric signals within it.	Angular or IMP		Empty cavity with visualized Left Fallopian tube ostium. On the right side, just above the tubal corner, the uterine cavity appears to be imprinted by a swelling.	Round, highly vascularized swelling (2-3cm) in the right fundus, extending to the emergence of the salpinx	Laparotomy + pathology	Laparotomy with excision of the gestational sac.	
75	Kiselev S.I [67]	2021	Russia	37/ spontaneous	Asymptomatic	Previous abortion(X2) and Hysteroscopic removal of submucosal myoma	No intrauterine pregnancy (IUP), round cystic structure at the border of the body of the uterus & right appendages. Follow up ultrasound: 13mm gestational (GS) in the thickness of the posterior uterine wall with fetal pole and yolk sac, but no fetal heartbeat. Color Doppler showed increased blood flow along the periphery of the GS.	Interstitial Ectopic pregnancy			Synechia in the upper 3rd of the cervical canal. On the left half of the uterine cavity, there is pronounced decidual reaction of the endometrium & an unchanged mouth of the left Fallopian tubes visualized. The right half of the uterine cavity was not visualized owing to extensive uterine fusions.	Laparoscopy + surgery	Laparoscopic hysterotomy with excision of the mass	
76	Reddy R [68]	2017	India	23/ spontaneous	Pelvic pain & hemorrhage	P3	Eccentric gestational sac (GS) with thick decidual reaction & a "ring of fire" appearance on color Doppler. Empty uterine cavity, no adnexal mass visualized		With contrast: Well-defined T1 isointense, T2 hypointense lesion in the anterior myometrium abutting the junctional zone & showing contrast enhancement. Empty ut with endometrial stripe seen separately.	empty cavity	Asymmetrically enlarged & swollen anterior uterine wall	MRI	Systemic methotrexate; then follow up until B-HCG is undetectable	
77	Fang-xiang Tang [69]	2021	China	34/ spontaneous	prolonged vaginal bleeding	G5P2	12mm lesion within the myometrium on right side of the uterine wall with enhancement on color Doppler	IMP		3D-MRI confirmed IMP		3D MR Reconstruction	Laparoscopic with resection of the mass	
78	Venkatesh M [70]	2020	India	35/ spontaneous	Lower abdominal pain	G2P1A0	Gestational sac in the myometrium close to the serosa with viable fetal pole.	IMP		Gestational sac (GS) with a hypointense fetal pole (FP) in the anterior myometrium and a T2 curvilinear hyperintense tract extending from the endometrial cavity to the GS.		MRI	Laparotomy with wedged resection of the gestational sac.	
79	Marotta M [37]	2012	Belgium	24/ spontaneous	Acute pelvic pain	Previous miscarriage	heterogeneous subserous 3.5 x 3.0 cm mass and regularly circumscribed.	Adenomyoma or IMP		Right lateral intramyometrial mass. T2-weighted 35mm heterogeneous mass at some distance from the uterine cavity. T1-weighted showed a discretely hyperintense mass. Right uterine horn not distorted by the mass.	Normal cavity & ostia	subserous 3cm mass at the Right side of uterus, below the utero-ovarian ligament with 50ml of blood in the pouch of Douglas	Pathology	Laparoscopic excision of the mass
80	Leyder M [71]	2010	Belgium	40/ ICS-ET	Asymptomatic	G2P0A1	Mixed echoes mass visualized in the left cornual part of the uterine wall within a previously necrotic fibroid. Color Doppler: hypervascular mass within the myometrium.				Empty uterus	Enlarged uterus with normal adnexa; no ascites	MRI	Multiple doses of systemic methotrexate
81	Kumtepe, Y [72]	2007	Turkey	38/ Ovulation induction + artificial insemination (IUI)	Asymptomatic	G2P0A0	Gestational sac (2.2cm) within the myometrium.	IMP	IMP				MRI	Multiple doses of systemic methotrexate with folinic acid
82	Sheerer DM [73]	2006	USA	36/ spontaneous	Vaginal bleeding	G2P2A0; Previous curettage	Anechoic sac-like structure surrounded by what appeared to be a myometrial mantle within the interstitial area, separated from the endometrium. Color Doppler: isolated highly vascular intramural lesion approximately 2cm in diameter.	Interstitial Ectopic pregnancy				Normal findings	Pathology	Hysterectomy (Choriocarcinoma)

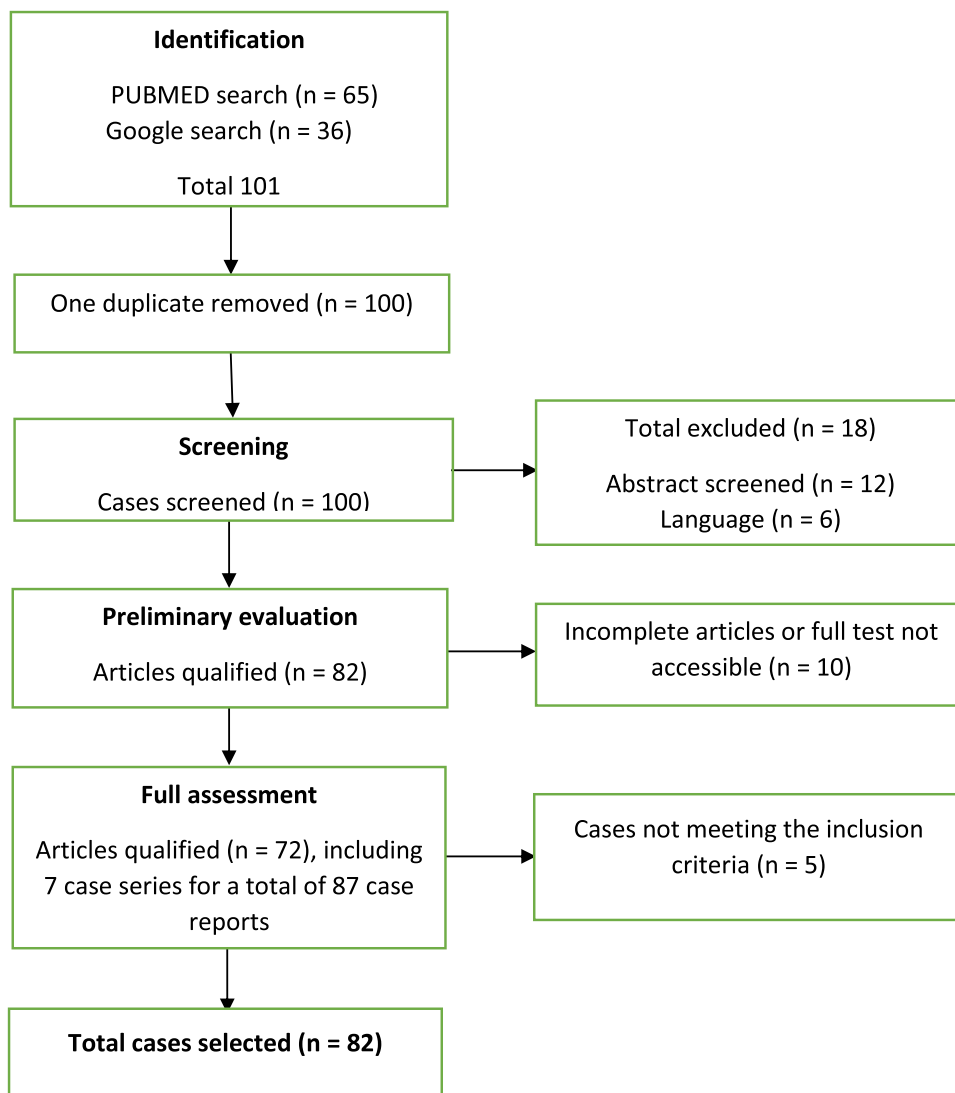


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the database search and selection process for cases and articles included in the study.

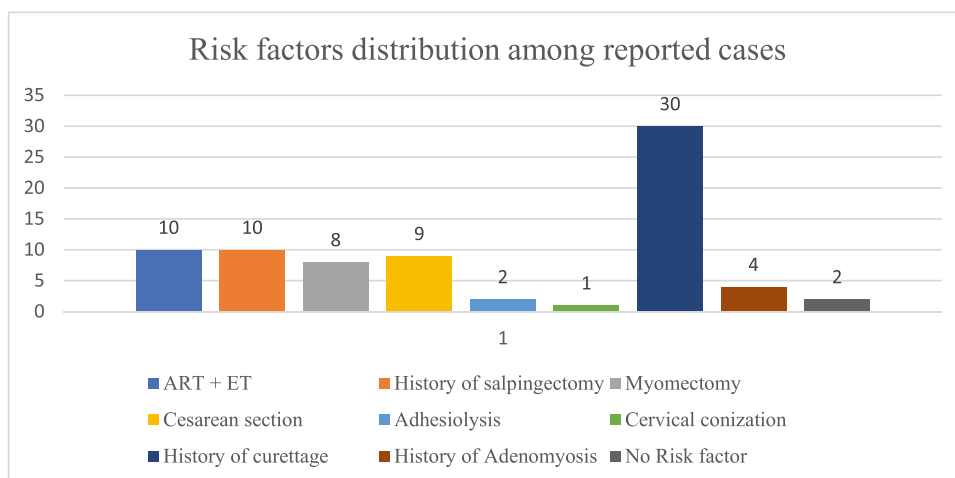


Fig. 2. Bar graph illustrating the most common risk factors for intramural ectopic pregnancy (IMP). ART+ET = assisted reproductive techniques with embryo transfer.

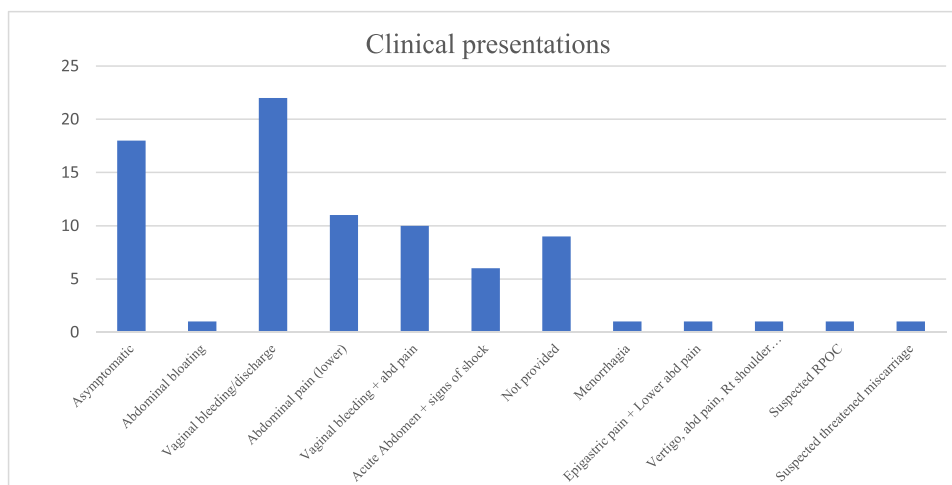


Fig. 3. Bar graph illustrating the most common clinical presentations of IMP. Abd = abdominal; RPOC = retained products of conception; Rt = right.

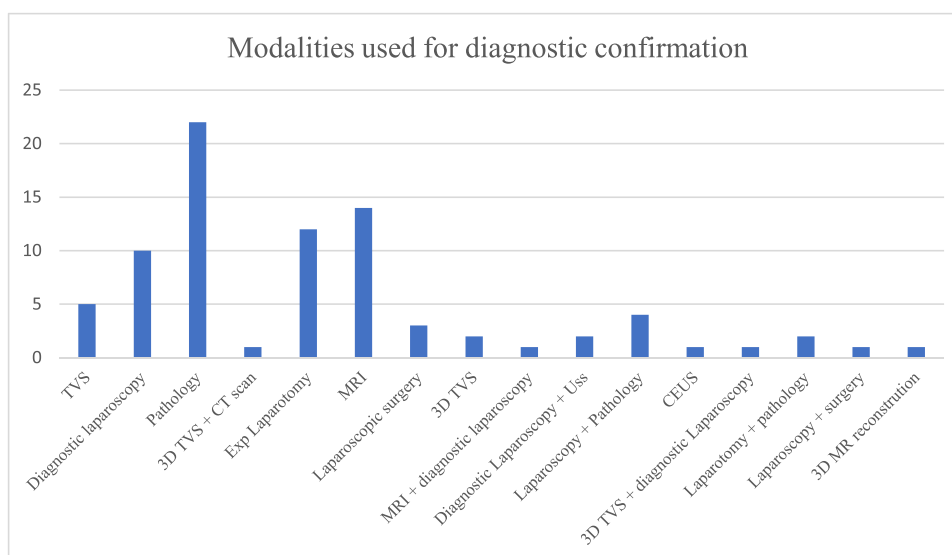


Fig. 4. Bar graph illustrating modalities commonly used to confirm a diagnosis of IMP. CEUS = contrast-enhanced ultrasound; TVS = transvaginal ultrasound; Uss = ultrasound.

Risk factors associated with the pathogenesis of IMP [Fig. 2] were history of curettage (36.58%), history of cesarean section (10.97%), history of salpingectomy (12.19% patients), ART-ET (12.19%), history of myomectomy (9.75%), and adenomyosis (4.88%). Interestingly, two reported cases had no predisposing risk factors [13,37].

To the best of our knowledge, this study is the first to identify a possible association between a history of salpingectomy and the development of IMP. Among the 10 patients (12.19%) with IMP who had a history of salpingectomy, eight (80%) had no other risk factor. The underlying pathophysiology of a potential link between IMP and salpingectomy remains to be elucidated. Mellouli and colleagues [58] reported a case of IMP following salpingectomy without providing more information on the possibility of a connection. Similarly, You and colleagues [33] reported a case of IMP implanted on a scar where the uterus was previously perforated by a dislodged intrauterine device (IUD).

5.2. Clinical presentation

IMPs present with a range of nonspecific signs and symptoms. Factors that influence the clinical course include the extent of myometrial involvement, the GA at the time of diagnosis, and the location of the GS

[1]. Vaginal bleeding and lower abdominal pain are the most common initial symptoms (Fig. 3). However, in our study, 18 patients (21.69%) were asymptomatic. IMP rupture presents as acute abdominal pain and/or signs of hypovolemic or hemorrhagic shock. This is most common in gestations exceeding 12 weeks GA [1,24,35,40,46,56,62,64]. Notably, although IMPs persisting beyond 12 weeks are uncommon and exceedingly rare beyond the second trimester, cases of IMPs with fetal survival have been reported; all of which required a cesarean section [34,75].

Two cases of biopsy-confirmed IMP with negative beta-HCG have been reported [28,76]. Dousias and colleagues [28] reported a patient with five-month menorrhagia who underwent a myomectomy after a diagnosis of “intramural myoma” was made on transvaginal ultrasound. Post-operative pathology findings were however those of an IMP. Similarly, Hsieh and colleagues [76] reported a woman with a five-month history of vaginal spotting who underwent curettage six months prior. Ultrasound showed an intramural cyst with embryo-like components. The diagnosis of IMP was made postoperatively after the biopsied cyst was confirmed to be an IMP. It is possible that in both cases, the IMP spontaneously got demised, but failed to resorb completely.

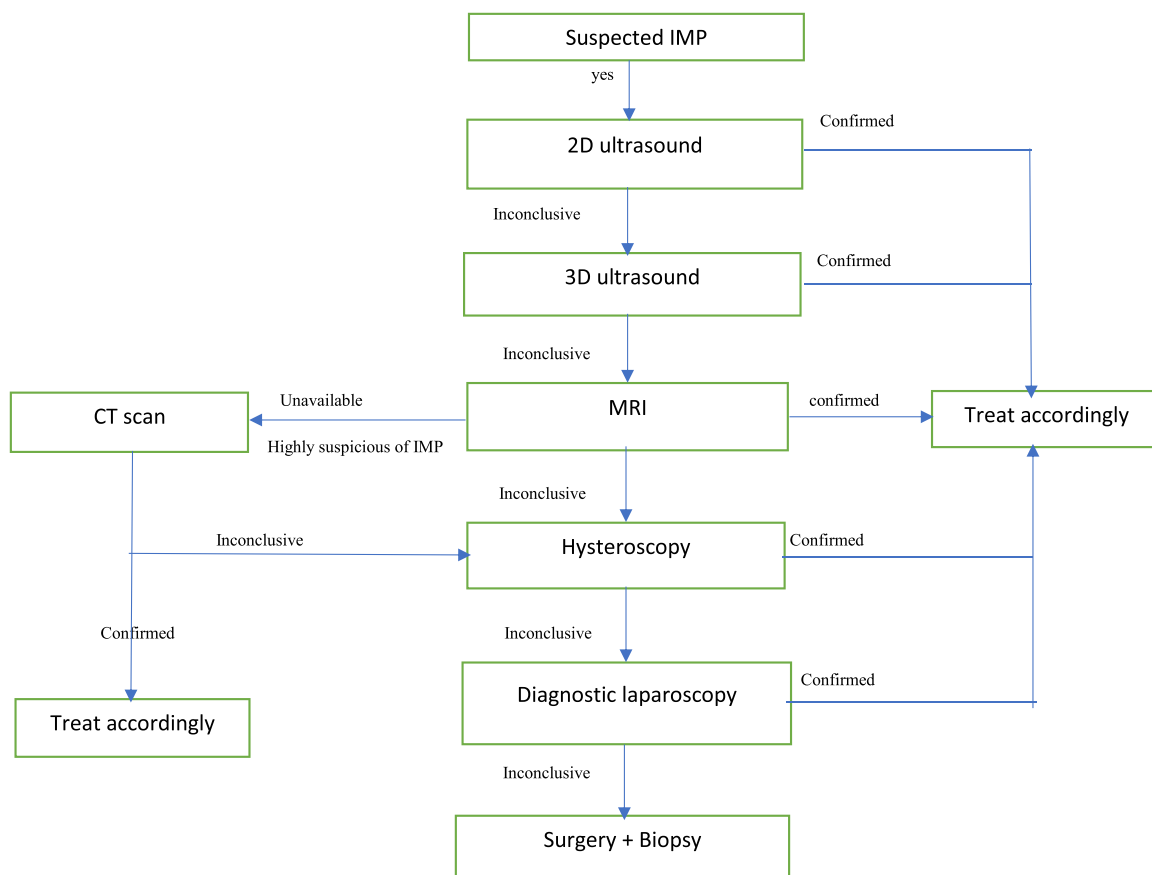


Fig. 5. Diagnostic algorithm for suspected IMP.

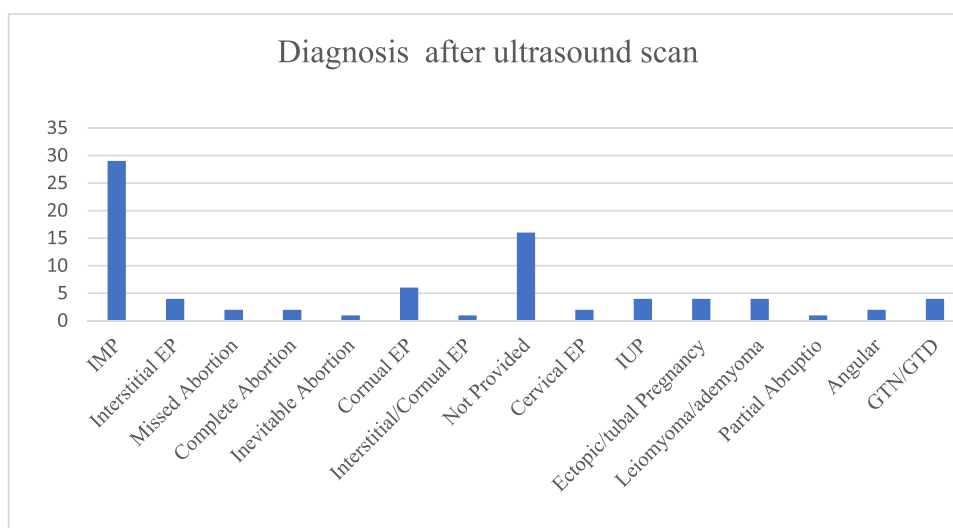


Fig. 6. Bar graph demonstrating diagnoses of suspected IMP following an ultrasound evaluation. EP = ectopic pregnancy; GTD/GTN = gestational trophoblastic disease/gestational trophoblastic neoplasm; IUP = intrauterine pregnancy.

Post-partum diagnosis of IMP has also been reported [1]. In this case, part of the retained placental products was partially embedded in the myometrium. In our opinion, this description is identical to that of placenta percreta. A clear differentiation of partial IMP [as described by Mentsa et al. [1]] from placenta percreta is necessary for clarification.

5.3. Diagnosis

Other types of EPs and spontaneous abortions present with symptoms similar to those of IMP (Fig. 8). To avoid false positive findings, it is important to consider other factors such as clinical history, physical examination, laboratory and imaging findings while making diagnostic assessments. In the absence of advanced diagnostic tools, especially ultrasound imaging, early diagnosis of IMP is challenging. Historically,

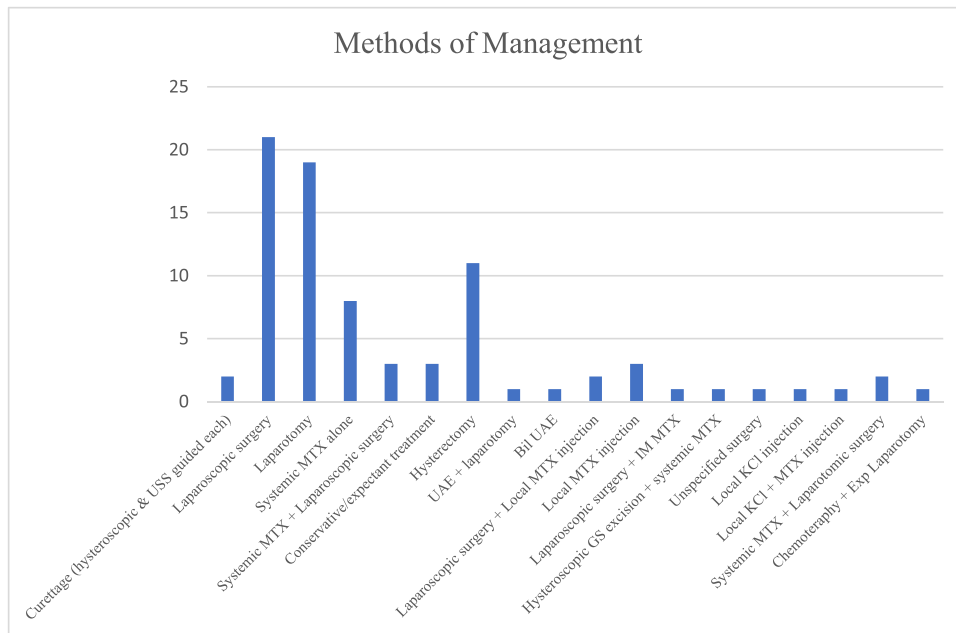


Fig. 7. Bar graph illustrating management strategies for IMP. Bil = bilateral; Uss = ultrasound.

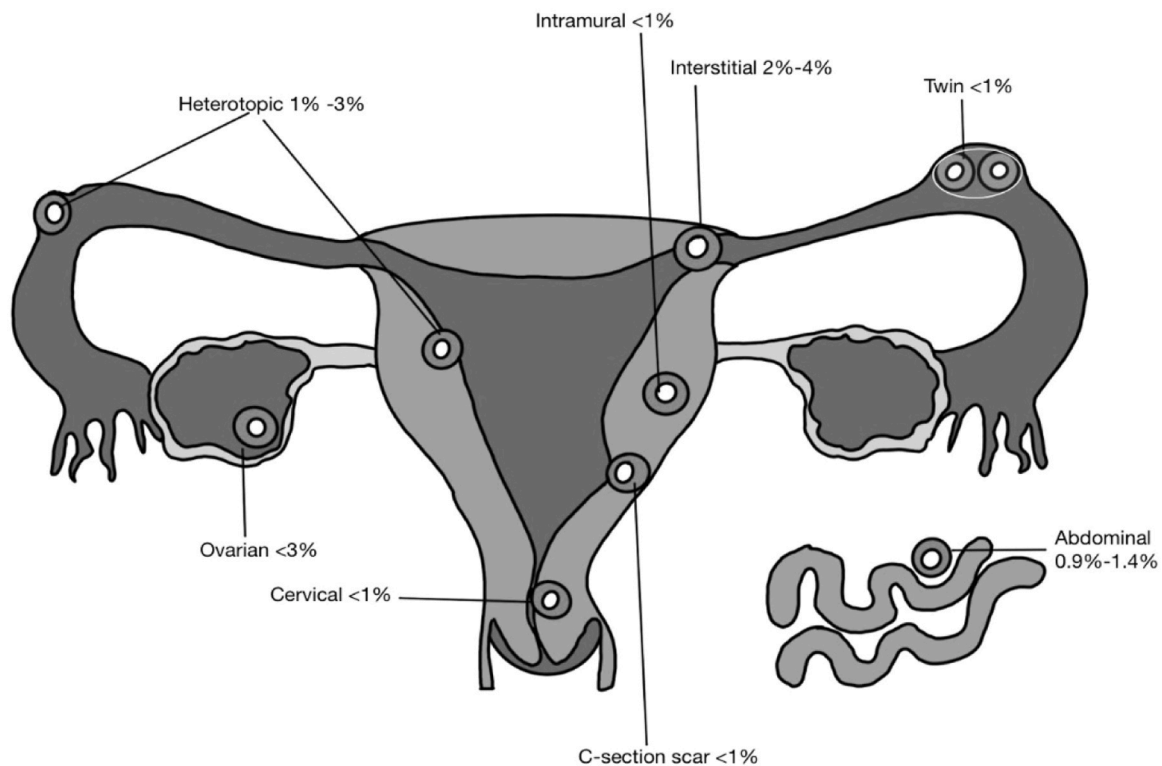


Fig. 8. Diagram illustrating locations and incidence of uncommon sites of ectopic pregnancy [Based on a model used by Chukus et al. [77]].

cases were diagnosed following laparotomy. In developed countries, ultrasound and MRI now play a central role in diagnosis.

Ultrasound is a safe, non-invasive and widely available diagnostic modality; mostly used as the first-line diagnostic tool. In our study, 29 cases (35.36%) of IMP were correctly diagnosed or strongly suspected after the initial ultrasound. The most commonly described ultrasound features were as follows:

1. Empty uterus and cervical canal with the endometrial cavity not connected to the GS.
2. GS (with/without a fetal pole), a mass or amorphous echoes partially or completely surrounded by the myometrium.
3. Thin myometrial serosal surface usually measuring 3 mm or less.
4. Asymmetrically enlarged uterus with distorted contour.
5. High myometrial arcuate or peripheral vascular flow with low resistance on Doppler ultrasound, sometimes described as “ring of fire”

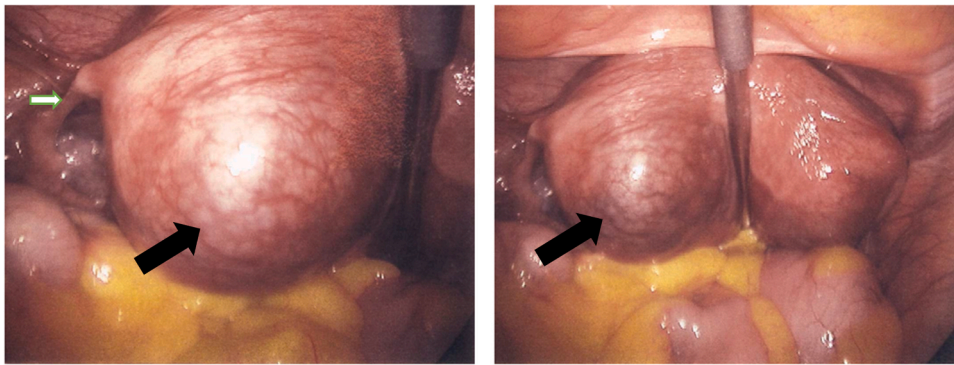


Fig. 9. Laparoscopy showing an IMP medial (black arrow) to the round ligament (white arrow). Note the hypervascularity of the bulging mass and the thin overlying serosa [from Ashraf et al. [23]]. Reused with permission.

In addition, a sinus tract connecting the GS to the endometrium was visualized using high-resolution 2D [20] and 3D [20,49] transvaginal ultrasounds.

IMPs that are collapsed, ruptured, or presenting with a GS without a fetal pole can easily mimic other conditions such as degenerating leiomyoma [12, 23, 27; 28] or gestational trophoblastic disease (GTD) [21, 43,57,61]. Sherer and colleagues [73] reported a case of intramural choriocarcinoma confirmed on biopsy.

Contrast-enhanced ultrasound (CEUS) has recently been used to confirm a suspected diagnosis of IMP. In a recent study, Liu and colleagues [78] described the following hallmark findings:

1. Early enhancement of the myometrial implantation site (about nine seconds post-injection), and that of a vessel-like area in the myometrium, indicating the myometrial origin of the GS blood supply.
2. The contrast agent enhanced for a long duration around the GS (between the eleventh to the twenty-eighth second after contrast agent's injection), and washed out later than the myometrium.
3. Clear delineation with minimal enhancement of the myometrial boundary between the GS and the endometrium during the late enhancement phase and the washout stage (about 29 s post-injection).

These findings are from a single case, and may vary with the GA. More studies need to be conducted to increase the knowledge about the diagnostic use of CEUS in IMP.

2D sonography cannot always clearly distinguish IMPs from interstitial or cornual EPs. However, with 3D sonography, there is a more accurate localization of the GS in relation to the uterine cornu or interstitium, and the endometrial cavity [2,14,49]. Furthermore, 3-D ultrasound in surface rendering mode enables a very clear visualization of the endometrial-myometrial junction, which facilitates the diagnosis of partial IMPs [79]. In our study, four (4.88%) cases involved the use of 3D ultrasound in their diagnostic evaluation [10,20,49,52].

Ruptured IMP typically presents with hemoperitoneum, characterized as a hypoechoic fluid collection with low-level internal echoes on ultrasound. The GS may be seen attached to or detached from the uterus, sometimes with the embryo or fetus floating within the abdomen.

MRI can be used to supplement or confirm the diagnosis following an ultrasound. Because of its excellent spatial resolution, it clearly demonstrates the endometrium-myometrium border and the relationship between the endometrial cavity and the GS. It has been postulated as the gold standard for diagnosing IMP [56,80]. In our review, MRI was used to evaluate IMP in only 18 cases (21.95%). This could be explained by the scarcity of MRI in many parts of the world, especially in developing countries [81–83]. Furthermore, there are many cases that were reported before diagnostic MRI became commercially available. On MRI, the GS is typically hyperintense on T2 weighted, and isointense or hypointense on T1 weighted images [12,68,70,71]. In addition, the GS

may be surrounded by tortuous vessels, which appear as tubular structures of high signal intensity [25] or signal voids [9]. Intramural GS or mass enhances on gadolinium contrast and the level and the distribution of the enhancement varies with the content. [25,68]. Furthermore, a connecting tract between the endometrial cavity and the GS presumably due to endometrial trauma can also be visualized and was reported in two cases [25,70].

CT scan utilization was reported in four cases. Although CT scan provides good spatial resolution, it should only be used under certain circumstances: a) when MRI is unavailable, b) when there is a very high index of suspicion, c) when only an amorphous mass or GS with a non-viable embryonic pole is seen on ultrasound. This is because of its high radiation dose and potential teratogenicity, especially in the first 8 weeks during organogenesis. In this study, CT findings were similar to those of USS and MRI. In addition, a mass with unclear flocculent enhancement in the uterine wall, reaching deep into the myometrium [43] and a mass with an obscured boundary [53] have been described. As preoperative ultrasonography, CT and MRI cannot exclude other types of EPs or GTD in some cases. In these situations, the diagnosis of IMP will be made using invasive methods such as hysteroscopy, diagnostic laparoscopy and postoperative biopsy.

Diagnostic hysteroscopy was carried out in 22 (26.83%) cases after an equivocal transvaginal ultrasound scan in most cases. Recurrently reported findings include:

1. Empty uterus with no GS visualized (100%)
2. Visualization of the Fallopian tubes' ostia, excluding tubal pregnancies (50%).
3. Uterine adhesions or fibrous tissues from previous instrumentation (13.64%)
4. Sometimes decidual hyperplasia/endometrial thickening or thinning. (31.82%)
5. Small bulge into the endometrial cavity. (18.18%)

Furthermore, Auer-Schmidt and colleagues [5] describe a false tract connecting the GS to the endometrial cavity visualized on hysteroscopy.

Diagnostic laparoscopy is usually the last in the chain of diagnostic evaluations before therapeutic surgical intervention. Findings include an asymmetrically enlarged uterus with a bulging or protruding mass. The mass is usually highly vascularized and covered by a very thin serosa that sometimes reveals the GS (Fig. 9). In addition, hemoperitoneum can be seen in cases of slowly leaking or ruptured IMP.

In cases where a questionable mass instead of a GS sac was visualized on imaging, the gold standard for diagnosis was histopathology after surgery. Findings were chorionic villi (with or without degenerative changes) surrounded by myometrial smooth muscles infiltrated by trophoblastic cells, plus no identifiable fallopian tubes.

5.4. Management and follow-up

The management of IMP depends on the clinical condition, age of the patient, plans for future children, serum β -hCG value, size and location of the mass as well as hemodynamic status [84]. GA also plays a key role in treatment decisions. Reported options include conservative/expectant treatment, local or systemic methotrexate, local potassium chloride (KCl) injection and surgery. Historically, the treatment option was surgery usually with hysterectomy as IMPs were diagnosed after they had ruptured or intraoperatively during a diagnostic exploratory laparotomy. Advances in imaging with ultrasound and MRI have made it possible to diagnose IMP at a very early stage. Successful conservative management in which no treatment was required for the IMP to resolve was reported in three cases [1,19,49]. However, the most commonly used management was the surgical approach; including laparoscopic or laparotomic GS resection or hysterectomy. 11 (13.41%) had a hysterectomy of which one had biopsy confirmed choriocarcinoma [73]. Successful treatment with Uterine artery embolization (UAE) [29] and hysteroscopic guided curettage [5] have been reported. After the surgery, methylene blue instillation was used in one case to confirm the presence of a fistulous tract communicating between the endometrial cavity and the IMP [10]. It is important to note that no major complication was reported with the various surgical treatments.

Medical management in the majority of cases, consisted of the use of local or systemic methotrexate (MTX). The successful use of local injection of KCl as a single agent [30] or with MTX [2] has been reported. Chemotherapeutic agents [Etoposide, Methotrexate, Actinomycin D, cyclophosphamide (MEA-CO)] have been described in cases of suspected intramural GTD/neoplasm pending the final pathology report [43,57]. Medical treatment requires follow-up for a long duration and in many instances fails, especially at advanced GA, necessitating surgery. The success of medical treatment reduces as the pregnancy progresses. In our study, out of the 19 who had medical treatment, 6 (31.58%) eventually underwent surgery owing to failure; for a success rate of about 68.42%. Treatment options that can be considered hybrid; involving the use of both surgical and medical management have also been described. After the surgical excision of the mass, local or systemic MTX is administered to discourage the growth of residual trophoblastic cells [8,16,20,63]. On the other hand, medical treatment can be given to shrink the mass or the GS before surgery is performed, hence, reducing the amount of bleeding and the size of uterine incision. However, in this study, most surgeries performed after a medical approach were as a result of treatment failure. Chida and colleagues described a case where bilateral UAE was performed three days prior to surgery [3]. Despite not expatiating the rationale for this approach, it is possible that using UAE to cut the blood supply of the IMP prior to surgery would make the mass shrink and reduce the amount of bleeding during surgery.

Because of the increased risk of IMP recurrence, women with preserved uterus following IMP removal surgeries should be advised to do an ultrasound scan as soon as the GS can be visualized (5–6 weeks) in all future pregnancies [1] to enable early diagnosis and treatment.

6. Conclusion

IMP is a rare but potentially lethal clinical entity. A significant proportion of patients are asymptomatic and have no known risk factors. Correlation of clinical history and imaging findings is vital to establishing a prompt diagnosis and reducing the risk of a catastrophic outcome.

Ultrasound plays a key role in establishing a diagnosis of IMP. However, in the setting of a positive pregnancy test, a GS or mass-like amorphous echoes partially or completely surrounded by myometrium is virtually pathognomonic. A serosal surface of the myometrium less than 3 mm thick in the body of the uterus should also raise suspicion for IMP. In some cases, MRI may be indicated to establish a definitive

diagnosis and for surgical planning. There are no defined clinical practice guidelines for the management of IMP. However, medical and/or surgical managements are nearly always required. Recognition of classic clinical and radiologic findings helps improve diagnostic accuracy and reduce morbidity and mortality among women presenting with IMP.

Declaration of Competing Interest

All three authors have NO conflict of interest to declare.

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