



## CASE REPORT AND LITERATURE REVIEW

# Intramural Pregnancy Misdiagnosed as Gestational Trophoblastic Neoplasia: Case Report and Review of the Literature

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### Abstract

**Purpose:** To date, only a few cases of intramural pregnancy have been recorded. We aim to report an uncommon case of intramural pregnancy misdiagnosed as gestational trophoblastic neoplasia, emphasizing that earlier surgical intervention may contribute to timely diagnosis and precise treatment.

**Methods:** Relevant articles published over the past five years were identified through a literature searching, and related references in those literatures were also manually searched to find additional articles.

**Results:** Nineteen cases in total including this report were reviewed. Most patients possessed a history of intrauterine operation or uterine surgery. Diagnoses were mainly made by imageological examinations. And surgical procedure tended to be the dominant treatment of such diseases.

**Conclusions:** Intramural pregnancy is considered to be the rarest type of ectopic gestation, where the gestational sac is completely encircled by myometrium. The non-specific clinical manifestations and non-uniform imageological criteria lead to the difficult diagnoses. However, earlier surgical management may contribute to timely diagnosis and precise treatment.

### Keywords

Gestational trophoblastic neoplasia, Intramural pregnancy, Management, Misdiagnosis

encircled by the myometrium of the uterus, separating from the endometrial cavity, fallopian tubes, or round ligament. It accounts for less than 1% of the total number of ectopic pregnancies. Little is known about exact etiology of intramural pregnancy. Prior intrauterine trauma such as myomectomy, dilatation and curettage, cesarean section and difficult *in vitro* fertilization and embryo transfer (IVF-ET) may cause microscopic sinus tract and resultant improper implantation. Besides, the embryo will migrate into the myometrium on account of adenomyosis, together with endometrial tissue. Increased trophoblastic activity and inappropriate decidualization may also be predisposing factors [1-5]. The most common clinical manifestations of intramural pregnancy contain vaginal bleeding and abdominal pain, which are exactly unremarkable. Although early detection is possible owing to imageological technology being advanced, the condition remains unknown to many clinicians and sonographers.

We hereby report a case of intramural pregnancy that was misdiagnosed as gestational trophoblastic neoplasia (GTN). The patient gave informed consent for this presentation. In addition, we have made a comprehensive review of published cases on PubMed from January 2015 to November 2020 in this report, nearly 18 cases were found by using the keywords: Intramural pregnancy.

### Case Report

A 33-year-old woman, gravida 4 para 1, presented

### Introduction

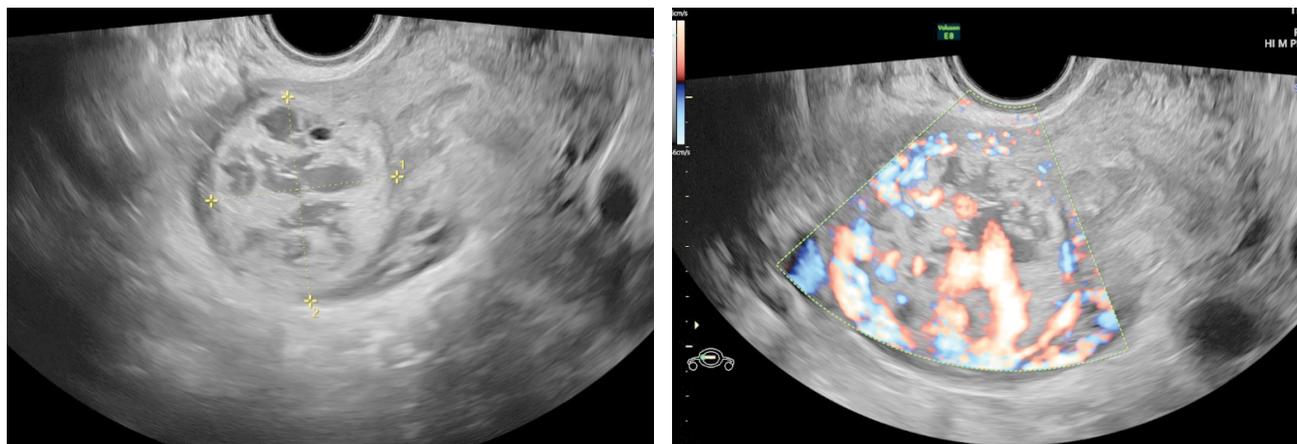
Intramural pregnancy is an extremely rare form of ectopic pregnancy, and refers to extrauterine conception whose gestational sac (GS) is partially or completely



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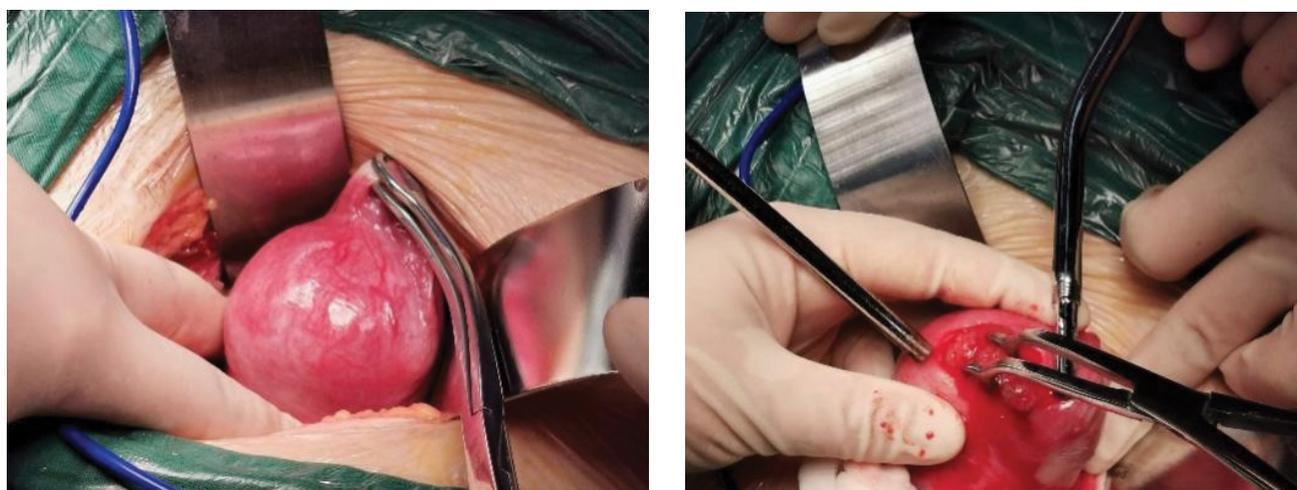
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A

B

**Figure 1:** (a) Transvaginal scan showed a mass with uneven echo in the right lateral wall of the uterus; (b) Doppler flow revealed abundant blood flow signals.



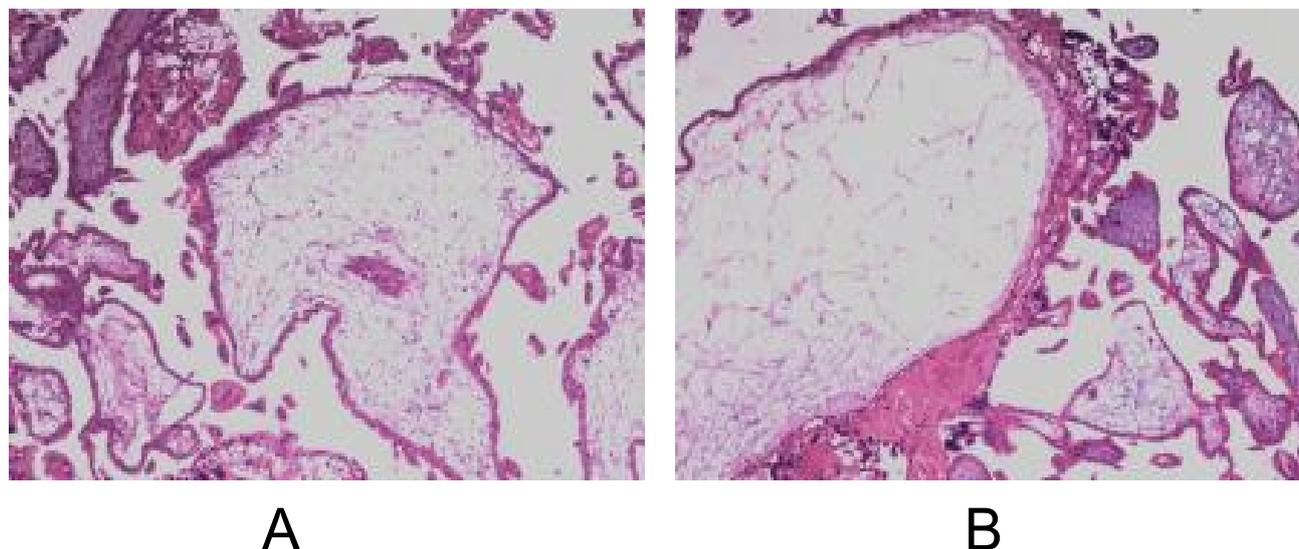
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**Figure 2:** (a) Laparoscopic intra-operative view showed the gestational sac protruding out from below the right horn of the uterus; (b) The chorionic villous tissues bulged out after a fusiform incision being made.

with vaginal bleeding, slight chest tightness and nausea, underwent a curettage at 5 weeks' gestation for incomplete abortion. While the level of serum  $\beta$ -HCG showed 39576 IU/L on post-surgery day and continued to rise during the following 2 weeks. On the day being transferred to our hospital, the level of serum  $\beta$ -HCG manifested 168208 IU/L, and the transvaginal sonography (TVS) denoted a mass with uneven echo and abundant blood flow in the right lateral wall of uterus, measuring 38 × 43 × 40 mm (Figure 1a and Figure 1b). On the second day of admission, the  $\beta$ -hCG value rose to 216338 IU/L, along with the mass growing to 41 × 44 × 52 mm. However, the chest computed tomography (CT) and craniocerebral CT revealed no abnormalities. Combining with the pathological result of her previous curettage which indicated necrotic villi, decidual tissue and some trophoblast cells, the preliminary diagnosis of

GTN and the decision to initiate EMA/CO chemotherapy regimen were made. Two days later, the serum  $\beta$ -HCG ascended to 225000 IU/L, and the ultrasound did not see the reduction of the mass. Due to the unsatisfactory effect, a surgical method was adopted on the tenth day. During the hysteroscopy exploration, a projection surrounded by abundant and tortuous vascular vessels was seen. Rapid pathology manifested the endometrium clamped by forceps did not contain any abnormal composition, leading to the exploratory laparotomy which showed a bulging mass measuring 50 × 50 mm with a purplish-blue-colored surface below the right horn of the uterus (Figure 2a). The chorionic villous tissues bulged out after a fusiform incision was made by a coagulation hook (Figure 2b), then the product of conception was completely removed and the wound was continuously sutured. Intraoperative pathology showed



**Figure 3:** (a and b) Histopathological observation showed the characteristic chorionic villi and the smooth muscle tissue was infiltrated with trophoblast cells.

oedematous villi and proliferous trophoblast cells, so the diagnosis of the hydatidiform mole was considered. Given such consequence, adjuvant chemotherapy continued after surgery. One day postoperatively the patient's  $\beta$ -hCG titer dropped to 37955 IU/L and then decreased to 711 IU/L on the tenth day, at which point she was discharged. A follow-up demonstrated the  $\beta$ -hCG level returned to normal. Ultimately, postoperative pathology in combination with immunohistochemistry analysis (P57+) confirmed chorionic villi surrounded by myometrium with no identifiable fallopian tube, validating the diagnosis of intramural ectopic pregnancy (Figure 3a and Figure 3b).

## Discussion

As is considered to be the rarest ectopic gestation, the incidence of intramural pregnancy is about 1:30000. Owing to its low incidence, it is easily misdiagnosed. According to Kirk, et al. [6], only 22 cases of intramural pregnancy from 2000 to 2012 all over the world. Our report summarizes the literature of intramural pregnancies since the year 2015, revealing 18 cases in all, the details of them are summed up in Table 1. There was only one patient led to a live birth [7], nevertheless, 10 patients preserved the fertility successfully.

The pathogenesis of intramural pregnancy still keeps unclear, various clinical conditions mirroring erstwhile traumas have been reported: Pelvic inflammation; endometrial defects; tiny sinus in the myometrium as a result of the previous operation; and pregnancy with adenomyosis. In our review, the age of patients ranged from 19 to 41-years-old. Except for seven patients, approximately three quarters (77.8%) had a history of uterine trauma [1-5,7-11], including artificial abortion (33.3%), cesarean section (21.4%) and myomectomy (14.3%). One cases (5.6%) experienced intrauterine device (IUD) placement, and two (11.1%) were the result

of adenomyosis or endometriosis. Furthermore, two patients (11.1%) became gravid with the aid of IVF-ET [7,11]. Similarly, the patient in our case had undergone several times of uterine curettage.

Vaginal bleeding (27.8%) and abdominal pain (16.7%) were the two relative common clinical manifestations in this summary, and our patient suffered from both of them. Such symptoms are unrepresentative so that late diagnosis or misdiagnosis could be made. Recently, advanced imageological examinations may matter by identifying trophoblastic invasion which extends beyond the endometrial-myometrial junction into the myometrium. Transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI) are common auxiliary techniques being performed, of which the latter is widely considered to be the gold standard [3,7]. Memtsa, et al. [12] even proposed a series of criteria for the sonographic diagnosis of intramural pregnancy. Apart from one case (7.1%) lacked related information, almost all patients (92.9%) underwent ultrasound examinations, some of whom accepted additional MRIs. Our case utilized both aforementioned auxiliary modalities, still more, added CT was performed for exclusion of choriocarcinoma which may metastasize to other organs. Regrettably, combining with the extremely high level of serum  $\beta$ -hCG, the diagnosis of GTN was primarily made.

Treatments of intramural pregnancy vary based on the exact location of the GS, depth of muscular invasion, patient's condition and desire to conserve fertility. If the uterus ruptures, hysterectomy is inevitable for the massive hemorrhage. If a clear diagnosis and hemodynamic stability can be achieved, conservative management could be a better choice. Injection of methotrexate (MTX) locally or systemically is the most convenient alternative, and studies have reported that ultrasound-guided intra-sac injection (USGI) of MTX is

Table 1: Details of intramural pregnancies identified in January 2015-November 2020.

Authors	Years	Gestational age	History of gynecology and Obstetrics	Manifestations	Imaging features	Management
Wang, et al.	2015	21	G3P1A1; D&C (x2) (second for intrauterine residues)	Vaginal bleeding	Ultrasound and MRI showed an empty endometrial cavity and a GS with a fetus implanted in the right posterior lateral side of the uterus fundus	Laparotomy with resection under temporary balloon occlusion of abdominal aorta
Nees, et al.	2015	32	D&C (x1)	Vaginal bleeding	-	Laparotomy with hysterectomy
Li, et al. [14]	2016	20	G1P0	-	A 14 x 14 cm GS on the right posterior lateral side of the uterus fundus	Laparotomy with resection under temporary balloon occlusion of transfemoral aorta
Bechev, et al. [11]	2017	28	G1P0; LSCS (x1); Salpingectomy of the left tube, Isthmic obstruction of the right tube; IVF-ET	-	A GS with presence of yolk sac measuring 1.2 cm were scanned in the posterior wall of the uterus, Completely surrounded by myometrium	US-guided MTX injected in the GS
Kong, et al. [10]	2017	20	G1P0; D&C (x1)	-	The GS at a distance from the cavity, With a compressed myometrium between the two of them; MRI showed the GS was embedded into the myometrium in the right posterior wall of the uterine	Laparotomy with resection under UAE
Mahmoud, et al. [1]	2017	33	G8P7; CS (x1)	Vaginal bleeding and Abdominal pain, Nausea and Vomiting	An empty uterine cavity and a 28 mm, Well-defined GS located in the anterior myometrium of the lower uterine segment	Laparotomy with resection
Mahmoud, et al. [1]	2017	34	G2P1;	-	Ultrasound and MRI indicated a mixed echogenic mass measuring 5.1 x 4.6 cm located within the posterior wall of the uterine fundus with an abundant blood supply	Hysteroscopy and laparotomy with resection following MTX-based chemotherapy
Liu, et al. [10]	2017	34	G2P1; D&C (x1); Laparoscopic surgery for endometriosis	-	A heterogeneous mass measuring 3.7 x 3.3 cm in the posterior wall, Extending to the uterineseros layer; MRI indicated an irregular signal area in the left wall within the myometrium of the uterus	Hysteroscopy and Laparoscopic resection
		19	G1P0; D&C (x1)	Vaginal bleeding and Vomiting	A heterogeneous mass measuring 4.2 x 2.9 cm in the left posterior wall of the uterus	Laparoscopic resection

	40	G4P0	Severe abdominal pain	A heterogeneous echogenic mass (5.4 x 4.4 cm) in the right side of the uterine wall, close to the corneal tissue, and the embryo bud not connected with the endometria	Hysteroscopy and Laparoscopic resection
Lyu, et al. [7]	26	G2P0; Right salpingectomy; IVF-ET (twin pregnancy)	-	Intrauterine pregnancy with another mass measuring 2.0 x 2.0 cm in the left cornua separate from uterine cavity and surrounded by musculature	Laparoscopic resection (another led to a live birth)
Vagg, et al. [2]	34	G2P2; Open Myomectomy (x1)	-	A GS measuring 8.0 x 7.9 x 7.0 cm within the myometrium of the right uterine cornua	Laparotomy, Hysterectomy and Bilateral salpingectomy
Yang, et al. [13]	31	-	-	A GS measuring 3.0 x 2.0 x 1.1 cm in the righthorn of the uterus surrounded by the myometrium	Hysteroscopy and Laparoscopic resection with injection of terlipressin (6U)
You, et al. [9]	35	G5P3; IUD (x1); Adenomyosis	Severe pelvic pain and Hypotension	A mass (7.0 x 5.0 cm) was located in the uterus	Laparoscopic resection
Zhang, et al. [3]	30	G1P1; CS (x1)	Vaginal bleeding	A mass measuring 4.0 x 3.0 x 3.0 cm was observed in the posterior wall below the left horn of the uterus	Laparoscopic resection with injection of terlipressin (6U) and MTX (50 mg)
Chaikof, et al. [8]	35	G2P2; D&C (x1); Asherman syndrome	-	The GS was located within 3 mm of the uterine serosa	Local resection
Liu, et al. [5]	28	G2P1; Right salpingectomy; IVF-ET	-	A ill-defined hypoechogenic structure with 14 x 13 mm in size was between the right ovary and the uterus contour	Hysteroscopy and Laparoscopic resection
Nees, et al. [4]	24	CS (x1)	-	A 4.3 x 3.5 cm mass containing a GS with a viable embryo was seen on the left side of the uterus	Laparotomy with uterine wedge resection
This report	33	G4P1; D&C (x1)	Vaginal bleeding, Slight chest tightness and Nausea	A mass measuring 38 x 43 x 40 mm with uneven echo located in the right lateral wall of uterus	Chemotherapy of EMA-CO, Hysteroscopy and Laparotomy with resection

D&C: Dilatation and Curettage; GS: Gestational Sac; LSCS: Laparoscopic Hysteromyomectomy; MTX: Methotrexate; IVF-ET: In Vitro Fertilization and Embryo Transfer; UAE: Uterine Artery Embolization; IUD: Intrauterine Contraceptive Device; CS: Cesarean Section

evaluated relatively more effective unless the  $\beta$ -HCG indicates an extraordinarily low concentration [11]. Local removal under laparoscope is always accepted when the GS can be observed through real-time exploration. Yang, et al. [13] suggested hysteroscopic resection is feasible as well, which depends on the distance between GS to uterine cavity or uterine serosa. If there exists uncertainty in minimally invasive surgery, an open laparotomy could be another option. Nevertheless, surgical strategy theoretically increases the danger of uterine rupture in the event of a future pregnancy. Furthermore, uterine artery embolization (UAE) and temporary balloon occlusion have been confirmed effective in embryo atrophy and absorption as well [14].

The majority of cases (55.6%) we reviewed accepted minimally invasive surgery with local resection, indicating the effectiveness and practicability in where advanced endoscopic expertise is available. One (7.1%) was amenable to USGI of MTX, and one (7.1%) was treated by expectant management for the desperately low level of serum  $\beta$ -hCG. In our report, EMA/CO chemotherapy regimen was adopted originally for suspect of GTN, a kind of malignant gynecological tumor caused by trophoblastic proliferation, yet the  $\beta$ -hCG level of which could far exceed that of intramural pregnancy. If the treatment cannot be distinctly decided, the surgical procedure should be considered, with which unnecessary chemotherapy could be avoided. Sun, et al. [7] described a similar case to the one here, owing to misdiagnosis and the implementation of chemotherapy, the patient was exposed to a series of side effects, including fever, fatigue, mouth ulcers, liver dysfunction and bone marrow suppression. Fortunately, our patient has promptly accepted surgery, confirming the diagnosis of intramural pregnancy and curing it ultimately.

## Conclusion

This case and review of the literature emphasize the challenge of recognizing intramural pregnancy. Early diagnosis plays a pivotal role in preventing complications, including uterine rupture, life-threatening hemorrhage and resultant hysterectomy. Atypical clinical presentations and indistinguishable imaging features are primary difficulties for medical professionals. The treatment should be individualized and combined, yet if intramural pregnancy is suspected, earlier surgical intervention may contribute to timely diagnosis and supervision. In addition, patients exposed to hazardous factors ought to seek medical attention early in their pregnancy. It is also vital to set up uniform diagnostic criteria and management guidelines.

## Disclosure

The authors declare no conflict of interest.

## Author Contribution

Lejing Zang: Project development, Data Collection, Manuscript writing; Yan Hu: Supervision.

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