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# Exaggerated placental site gestational trophoblastic disease: A case report

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**Abstract:**

Gestational trophoblastic diseases (GTDs) represent a unique group of lesions with an abnormal proliferation of trophoblasts. GTD can be divided into molar lesions and nonmolar lesions. Partial and complete hydatidiform moles and invasive moles are under molar lesions, whereas non-molar lesions include choriocarcinomas and lesions that are derived from intermediate trophoblasts (ITs). These IT can be from the implantation site (exaggerated placental site [EPS] and placental site trophoblastic tumor) or from the chorionic type (placental site nodule and epithelioid trophoblastic tumor). EPS is a relatively uncommon form of GTD. It is a challenging condition for clinicians to diagnose because of the limited number of reported cases. From 1990 to April 2022, there were only 25 case reports published internationally, and this is the first local case report. Implantation site ITs (ISITs) are difficult to distinguish histologically. Immunohistochemical staining such as Ki-67 can improve diagnostic accuracy by differentiating ISIT. Ki 67 will show staining of <1% in EPS. This is the case of a 25-year-old patient, G6P5 (5005), who experienced vaginal bleeding associated with pelvic and hypogastric pain after 13 weeks of missed menses. She was diagnosed with a molar pregnancy and underwent an emergency total abdominal hysterectomy with bilateral salpingectomy due to severe uterine bleeding. Histopathologic studies in this case showed diffuse and infiltrative growth of atypical monomorphic ITs arranged in sheets and cords, infiltrating and separating myometrial fibers. The uterine blood vessel wall was replaced with fibrinoid deposition, with areas of hemorrhages and necrosis. There were also chorionic villi. The histopathological findings revealed GTD arising from ITs, specifically EPS. This article describes the clinical presentation, diagnostic procedure, and management, together with histopathological observations and a review of related literature, of this rare GTD.

**Keywords:**

Exaggerated placental site, gestational trophoblastic disease, intermediate trophoblast, Ki 67

## Introduction

Gestational trophoblastic disease (GTD) is a group of tumors defined by abnormal trophoblastic proliferation.[1] Trophoblastic stem cells develop along the two lines of differentiation: Villous and extravillous. Hydatidiform pregnancies and choriocarcinomas are derived from villous trophoblasts, which are composed mostly of cytotrophoblast and syncytiotrophoblast.[2] Extravillous trophoblasts are composed of implantation site intermediate trophoblasts (ISITs), specifically: Exaggerated placental site (EPS) and placental site trophoblastic tumor (PSTT) and those from the chorionic-type IT, namely: Placental site nodule (PSN) and epithelioid trophoblastic tumor (ETT).[1]

EPS and PSN are nonneoplastic lesions. Neoplasms with the potential for local invasion and metastasis are PSTTs and ETTs.

This article aims to discuss EPSs clinical presentation, diagnostic procedure, and management, together with its histopathological observations and evaluation of past literature on this rare GTD.

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## Case Report

This is the case of M. A., 25 years old female, single, from Paranaque City, admitted in our institution on February 10, 2022, due to acute vaginal bleeding.

The patient had a history of childhood bronchial asthma and allergies to seafood. She had no history of hypertension, diabetes mellitus, or other medical problems and no previous hospitalizations or surgeries.

Her family medical history revealed that her maternal side had hypertension and heart disease.

The patient was single, a high school undergraduate, and unemployed. She was a nonsmoker and an occasional alcoholic beverage drinker. Her first sexual contact was at the age of 17 years with one nonpromiscuous sexual partner. She had a history of combined oral contraceptive use for 2 years. She had no history of sexually transmitted diseases.

The patient had her menarche at 13 years of age with regular monthly intervals lasting for five days, soaking three pads per day in a moderate amount with associated dysmenorrhea during menses. She had a resumption of menses a month after her last vaginal delivery and it occurred regularly.

This was the patient's sixth pregnancy; the previous five pregnancies were carried to term, delivered through normal spontaneous delivery without any fetomaternal complications, and were all presently living. Her last delivery was in April 2021.

She had been amenorrheic for 13 weeks up until 6 days before her admittance, when she started having moderate vaginal bleeding that soaked four pads per day for 5 days while also causing hypogastric pain and the passage of meaty material.

Three days before admission, vaginal bleeding was still present, along with a documented fever of 39°C, anorexia, and vomiting. She self-medicated with a paracetamol 500 mg tablet, which afforded relief. A consultation was done at a Lying-in Clinic in Las Pinas, and a pregnancy test revealed a positive result. A transvaginal ultrasound was requested. She was then referred to the hospital of her choice due to pallor and vaginal bleeding.

On the day of admission, she was still experiencing vaginal bleeding, now accompanied by generalized weakness, which prompted a consult at our institution.

On admission, the patient was awake, conscious, coherent, pale, weak, and wheelchair-bound. Vital signs were stable, with a blood pressure of 110/70 mmHg, a heart rate of 100 beats per min, a respiratory rate of 20 cycles per min, and a temperature of 36.2°C.

A physical exam, centered on the abdomen, revealed flabby, normoactive bowel sounds that were soft and non-tender. On speculum examination, internal examination, and bimanual examination, there was normal smooth cervix and parous genitalia. The cervix measured 3 cm × 2.5 cm, was smooth, had no lesions, and was open with moderate vaginal bleeding. The uterus was movable and enlarged to 14–16 weeks size without adnexal mass or tenderness.

The use of laboratories and other diagnostic techniques was made. A transvaginal ultrasound [Figure 1] performed in another facility showed that the uterus was anteverted and measured 6.7 cm × 7.2 cm × 5.2 cm, with a regular shape and homogeneous echo pattern. The cervix was 3.2 by 3.1 by 2.1 cm in size. The stroma was homogeneous. The endometrium was thickened with cystic gaps and hyperechoic echogenicity, showing a snowstorm pattern. The thickness of the endometrium was 26.4 mm. The endomyometrial junction was intact. The right ovary measured 2.4 cm × 2.4 cm × 1.5 cm and was visible lateral to the uterus. The left ovary was visible next to the uterus and was normal in size and echo pattern, measuring 2.6 cm × 2.4 cm × 1.8 cm. No adnexal mass. There was no free fluid in the cul-de-sac. The sonological impression was a slightly enlarged anteverted uterus with thickened cystic and hyperechoic endometrium, a hydatidiform mole, normal ovaries, no adnexal mass, and no fluid in the cul-de-sac. Baseline Beta human chorionic gonadotropin (HCG) showed 10, 000 mIU/mL. A complete blood count showed very severe anemia with hemoglobin of 4 g/dL [Table 1]. The chest radiograph was unremarkable.

Admitting diagnosis was G6P5 (5005) Molar Pregnancy, 13 5/7 weeks AOG, Anemia, very severe; Grandmultiparity.

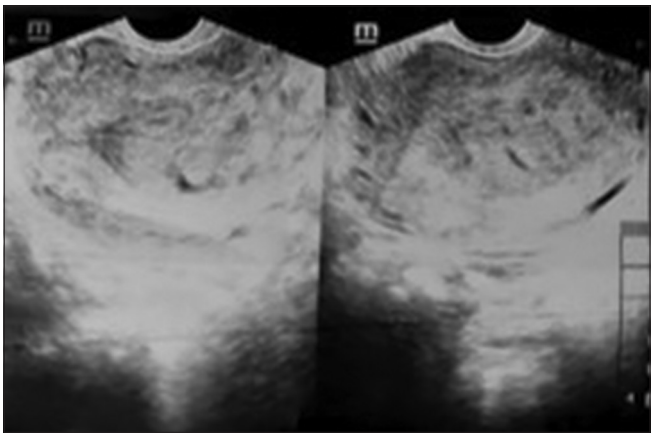

**Figure 1:** Transvaginal sonography showing slightly enlarged anteverted uterus with thickened cystic and hyperechoic endometrium to consider hydatidiform mole

Preoperatively, 4 units of packed RBC were transfused to correct the anemia. At that time, the patient was profusely bleeding and not desirous of a future pregnancy. The patient underwent emergency exploratory laparotomy, total abdominal hysterectomy, and bilateral salpingectomy under general anesthesia.

On laparotomy, the uterine corpus was slightly enlarged, measuring 8.5 cm × 8 cm × 5 cm, while the cervix was smooth and glistening, measuring 3 cm × 2.5 cm × 4 cm [Figures 2 and 3]. On a cut section, polypoid tissue was admixed with blood, and focal areas of hemorrhages were seen in the fundal area [Figure 4]. The anterior and posterior myometrium both measured 3 cm. The uterine cavity measured 6 cm in length, and the endocervical cavity measured 3 cm long. The endometrial thickness was 1 cm. The right fallopian tube measured 5 cm × 0.5 cm, while the left fallopian tube measured 5 cm × 1 cm [Figures 3 and 4]. Bilateral ovaries were grossly normal and were left behind.

The patient's postoperative course was unremarkable. Post-evacuation monitoring of serum Beta HCG was requested for the patient to assess if there was a postmolar trophoblastic disease. Serum Beta HCG was taken 7 days after surgery, which revealed 177.6 miU/mL and was undetectable 8 weeks postoperatively.

**Table 1: Complete blood count results**

| Test | On admission | Postoperative day 5 |
|---|---|---|
| Hgb | 4 | 11.3 |
| Hct | 0.12 | 0.36 |
| RBC | 1.53 | 4.41 |
| MCV | 79 | 81 |
| MCH | 26 | 26 |
| MCHC | 0.33 | 0.32 |
| WBC | 18.5 | 11.4 |
| Neutrophils | 86 | 77 |

Hgb: Hemoglobin, Hct: Hematocrit, RBC: Red blood cell, WBC: White blood cell, MCV: Mean corpuscular volume, MCH: Mean corpuscular Hgb, MCHC: MCH concentration

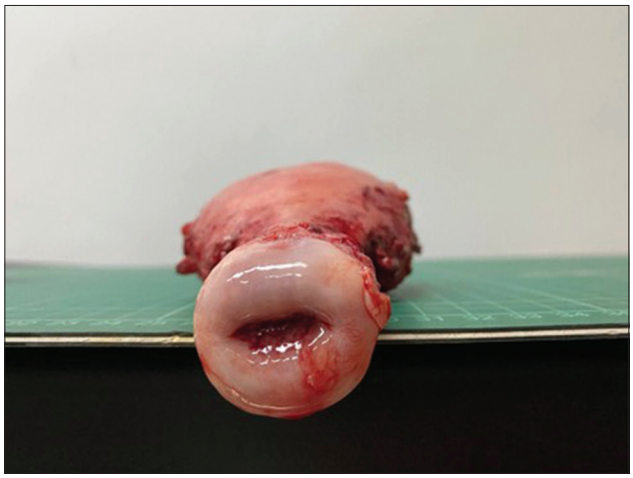

**Figure 2:** Ectocervix was smooth and glistening measuring 3 cm × 2.5 cm × 4 cm

The initial histopathology result revealed Gestational Trophoblastic Neoplasia. The considerations were EPS, PSTT, and ETT. Histopathologic studies in this case showed diffuse and infiltrative growth of atypical monomorphic ITs arranged in sheets and cords, infiltrating and separating myometrial fibers [Figures 5 and 6]. The uterine blood vessel walls were replaced with fibrinoid deposition, with areas of hemorrhages and necrosis [Figures 7 and 8]. There were also chorionic villi [Figure 9]. Infiltrative growth patterns with atypia and necrosis are common characteristics of neoplasms.

To validate the diagnosis, immunohistochemistry staining was carried out. The cells of interest had zero Ki-67 immunostaining, which is consistent with the diagnosis of an EPS [Figure 10]. The final histopathology result was an EPS [Figure 11], and due to its benign nature, no specific management, further workup, or monitoring was done.

## Discussion

EPS is rare, with a total of 25 reported cases from 1990 to April 2022, 14 case reports published (in English) taken from PubMed, 11 reported cases in various literature, and this is the first case reported locally (POGS PNSS).

In the past, EPS was called syncytial endometritis. In 1910, Ewing classified syncitial endometritis as chorionepithelioma.[3] The World Health Organization (WHO) coined the term "EPS," wherein lesions are noninflammatory, not limited to the endometrium, and the constituent cells are not syncytial.[4]

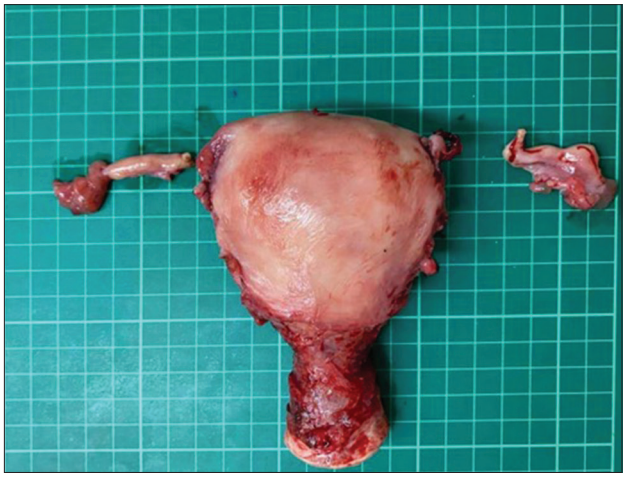

**Figure 3:** Uterus is pear-shaped, red to pinkish with smooth contour measuring 8.5 cm × 8 cm × 5 cm. No mass seen. Right fallopian tube is a red to pinkish fimbriated tubular structure measuring 4 cm × 2 cm × 0.7 cm. Left fallopian tube is a red to pinkish fimbriated tubular structure measuring 5 cm × 2.5 cm × 0.6 cm

EPS arises from the ISITs. ITs were named in this manner because they were considered intermediate in differentiation between cytotrophoblasts and syncitiotrophoblasts. ISITs are important for the maintenance of pregnancy. During early gestation, it infiltrates the decidua and invades the myometrium and spiral arteries, a physiologic process required to establish the maternal-fetal circulation. Physiologically, only the upper half of the myometrium is invaded by these cells during the first trimester, and they regress progressively over a period of time.[4]

In an extremely rare condition called EPS, ISIT infiltrates the myometrium exuberantly. When the IT infiltrates exaggeratedly into the myometrium, failing to regress or involute, the condition is called an EPS.[5] The exact underlying mechanism of the exaggerated number of IT in EPS remains to be determined. This may be due to the rapid cell cycle progression of IT in the trophoblastic columns or the suppression of apoptosis of IT in the deep implantation site.[6] There are no further studies quantifying the amount and extent of trophoblastic infiltration at different stages of normal gestation.[7]

Clinical presentation based on the 25 published case reports [Table 3] showed that the age group was between 15 and 55 years old. Antecedent pregnancy can be from ectopic pregnancy, abortion, molar pregnancy, or normal pregnancy. Seventeen out of 25 cases presented with continuous uterine bleeding. Other symptoms reported are abdominal pain, uterine atony, dyspnea, and nausea. In the index patient, she had vaginal bleeding associated with pelvic and hypogastric pain 13 weeks after missed menses. The initial diagnosis was a molar pregnancy.

In managing GTD, baseline laboratory examinations and imaging should be done. Laboratory examination includes pregnancy test, baseline serum Beta HCG, complete blood count with differential and platelet counts, liver function test, renal test, thyroid function test and urinalysis. Beta HCG in the 25 cases reviewed [Table 3] ranges from 6 mIU/mL to as high as 279,000 mIU/mL if associated with molar pregnancy. In the review of the literature, imaging studies include ultrasonography, magnetic resonance imaging (MRI), computed tomography scan, and hysteroscopy. Five of them showed a uterine mass, and six case reports presented with increased vascularity. The imaging studies were not specific for diagnosing EPS but may aid the clinician in the evaluation of the pelvis. In our patient, all the laboratory examinations mentioned above and transvaginal ultrasound were done [Tables 1, 2, 4, 5 and Figure 1]. The initial serum Beta HCG level was 10, 000 mIU/mL with an ultrasound finding of a slightly enlarged anteverted uterus with thickened cystic and hyperechoic endometrium to consider a hydatidiform mole. Serum Beta-HCG was taken 7 days after surgery, which revealed 177.6 miU/mL and was undetected 8 weeks postoperatively [Figure 12].

Gross findings in the review of literature revealed that 13 out of 25 case reports showed no evidence of a mass, while 12 cases presented with a uterine mass. Histopathologic findings in EPS are composed of a monomorphic ISITs that had an infiltrating growth pattern, abundant multinucleated cells, no mitosis with associated chorionic villi, and a Ki-67 labeling index of <1%.[8,9]

In our patient, we noted polypoid tissue with focal hemorrhages measuring 3.5 cm × 2.5 cm invading <50% of myometrium [Figure 4]. Histopathological studies in this case showed diffuse and infiltrative growth of atypical monomorphic ITs arranged in sheets and cords, infiltrating and separating myometrial fibers (splitting) [Figures 5 and 6]. The uterine blood vessel walls were replaced with fibrinoid deposition with areas of hemorrhages and necrosis [Figures 7 and 8].

**Table 2: Blood chemistry**

| Test | Normal value | Result |
|---|---|---|
| Urea nitrogen | 2.5–7.5 mmol/L | 2.3 |
| Creatinine | 53–106 umol/L | 63.2 |
| SGOT (AST) | 0–37 U/L | 17 |
| SGPT (ALT) | 0–41 U/L | 13 |
| Potassium | 3.5–5.5 mmol/L | 3.46 |
| Sodium | 135–145 mmol/L | 140.8 |
| Ionized calcium | 1.1–1.5 mmol/L | 0.97 |

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamate pyruvate transaminase, AST: Aspartate aminotransferase, ALT: Alanine transaminase

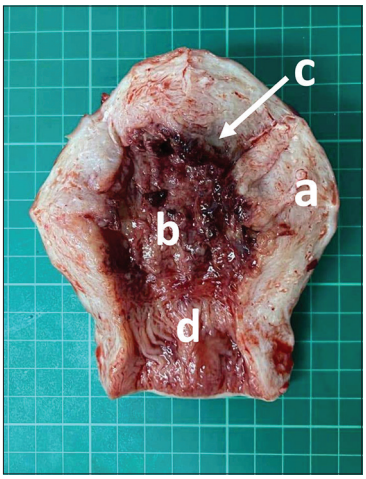


**Figure 4:** Cut section of the uterus and cervix. (a) Uterus has a white to red myometrium measuring 3.0 cm thick, (b) endometrial canal is 5 cm long with red to brown polypoid tissue with focal hemorrhages measuring 3.5 cm × 2.5 cm. Endometrial thickness is 1.0 cm, (c) grossly the polypoid tissue invades <50% of the myometrium (white arrow), (d) endocervical canal has a tan red herring bone mucosa measuring 4.0 cm long

**Table 3: Clinical courses of exaggerated placental site**

| Published year | Authors | Age of patients/OB score | Type of (antecedent pregnancy) | Gestational age of (antecedent pregnancy) | When the lesion of clinical symptom was recognized | Clinical symptoms and features | Gross lesion | Initial beta HCG | Final beta HCG | Initial diagnosis | Imaging | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1996 | Kase *et al.*[16] | 44<br>G5P2 | Cervical pregnancy | 7 weeks | During pregnancy | Continuous uterine bleeding and abdominal pain | No mass | NM | NM | GTD | US: 40 mm cystic mass located at the uterine cervix | Hysterectomy |
| 1999 | Menczer *et al.*[17] | 48<br>NM | Molar pregnancy | 9 weeks | 34 days after the second curettage | No symptom, increase of beta HCG | 10 mm of nodule in the uterine cavity | 1300 IU/mL (serum) | NM | GTD | DNA | Hysterectomy |
| 2003 | Nigam and Dass[18] | 40<br>G7P5<br>Abortion 2 | Abortion | Not mentioned | Not mentioned | Markedly raise of beta HCG, uterine bleeding with clots for a day | Bulky mass in the uterus | 15,855 IU/mL (urinary) | 107 IU/mL (immediate postoperative) | Chorio carcinoma | NM | Hysterectomy |
| 2008 | Stolnicu *et al.*[19] | 55<br>G6P4<br>Abortion 2 | Normal pregnancy | Term pregnancy | 15 years after the delivery | Massive uterine hemorrhage | 20 mm of flat plaque like lesion | NM | 8.8 IU/L 2 months after surgery | AUB | NM | Hysterectomy |
| 2008 | Hasegawa *et al.*[15] | 39<br>G3P2 (2012) | Induced abortion | 7 weeks | 1 week after the D and C | No symptom | 36 mm of lesion on the anterior wall of the uterus | 20 mIU/mL (serum) | 0.4 mIU/mL(3weeks postoperative) | GTD | US: Echogenic lesion in the uterine cavity measuring 36 mm in maximum diameter<br>MRI: Heterogeneous pattern of high and intermediate signal intensities. The boundary between the tumor and myometrium was irregular and the junctional zone was unclear | Hysterectomy |
| 2010 | Yeasmin *et al.*[5] | 33<br>NM | Normal pregnancy | Term pregnancy | 7 months after the delivery | Irregular uterine bleeding, endometrium | No mass | 3.3 mIU/mL (serum) | Undetectable | PSTT | US: Anechoic lesion on the posterior wall of the uterus involving both the endometrium and myometrium<br>MRI: Enlarged uterus with a slightly high-signal-intensity mass at the periphery of the posterior wall that showed mild gadolinium enhancement. There was also disruption of the integrity of the junctional zone | Hysterectomy |

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**Table 3: Contd...**

| Published year | Authors | Age of patients/OB score | Type of (antecedent pregnancy) | Gestational age of (antecedent pregnancy) | When the lesion of clinical symptom was recognized | Clinical symptoms and features | Gross lesion | Initial beta HCG | Final beta HCG | Initial diagnosis | Imaging | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2011 | Harada *et al.*[20] | 43<br>G4P3 | Induced abortion | 7 weeks | 41 days after the D and C | Continuous genital bleeding | 45 mm of polyp attached to the protruding lesion of the uterus | 126.1 mIU/mL | Undetectable after 4 weeks | Placental polyp | US: 4.5 cm ×1.8 cm bulky tumor with pulsatile blood flow from the uterine wall into the mass<br>MRI: Demonstrated a polyp-like mass attached to the anterior uterine corpus. At the attached area, a mass was prominently enhanced on contrast-enhanced T1 weighted image | Hysterectomy |
| 2012 | Akbayir *et al.*[21] | 24<br>NM | Normal pregnancy | Term pregnancy | At CS | No symptom | 30 mm of polypoid well-shaped smooth lesion on the uterine wall | DNA | DNA | Normal pregnancy | NM | CS delivery then resection |
| 2012 | Chen *et al.*[22] | 34<br>G1P0 | Fetal death, placenta previa | 24 weeks | At fundal hysterectomy (CS) | No symptom | 30 mm of nodular mass at the uterine wall | 9000 IU/mL | NM | Fetal death, placenta previa | US: Demised fetus and bulky placenta, with multicystic sonolucent spaces in the lower half of enlarged placental parenchyma. Doppler US shows hypervascularity with low resistance turbulent flow surrounding the echogenic uterine lesion<br>MRI: Accumulated flow voids just under the central part of the placenta. Well defined area with high to intermediate heterogenous signal intensity on T2 weighted MRI | Resection at the operation methotrexate ×2 dose |

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**Table 3: Contd...**

| Published year | Authors | Age of patients/OB score | Type of (antecedent pregnancy) | Gestational age of (antecedent pregnancy) | When the lesion of clinical symptom was recognized | Clinical symptoms and features | Gross lesion | Initial beta HCG | Final beta HCG | Initial diagnosis | Imaging | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2012 | Erdogan *et al.*[23] | NM G2P1 | Normal pregnancy | Term pregnancy | At CS | Heavy uterine bleeding with atonic uterus, diagnosed EPS based on pathology | No mass | NM | NM | Postpartum hemorrhage from uterine atony | NM | Hysterectomy |
| 2013 | Liu *et al.*[24] | 30 (DNA) | Breech presentation | Term pregnancy | At CS | Heavy uterine bleeding with atonic uterus, diagnosed EPS based on pathology | No mass | DNA | DNA | Breech presentation | DNA | Supravaginal hysterectomy |
| 2014 | Takebayashi *et al.*[25] | 35 G2P2 | Normal pregnancy, retained placenta | Term pregnancy | After the placental delivery | Severe uterine bleeding with atonic uterus, diagnosed EPS based on pathology | No mass | NM | NM | Retained placenta | NM | Supravaginal hysterectomy |
| 2014 | Ozdemir *et al.*[13] | 26 G3P1 | Molar pregnancy | 6 weeks | After molar evacuation | Nausea, heterogeneous mass with solid and cystic fields was seen in uterine cavity | 10 cm ×7 cm heterogeneous mass with solid and cystic fields was seen in uterine cavity | 279,000 mIU/mL | 6700 mIU/mL in the first 4 weeks followed by increasing measurement. Remission was achieved after 3 weeks single agent methotrexate | Molar pregnancy | US: 10 cm ×7 cm heterogeneous mass with solid and cystic fields was seen in uterine cavity | Mole evacuation and single agent methotrexate weekly |
| 2014 | Gupta *et al.*[26] | 26 G3P3 (3003) | Normal pregnancy | Term pregnancy | 10$^{th}$ day postpartum | Heavy uterine bleeding. Diagnosed EPS based on pathology | An irregular mass of around 2 cm ×2 cm was seen arising from the posterior wall of the uterus | NM | NM | Postpartum hemorrhage | US Doppler: Normal grossly with increased vascularity | Hysterectomy |
| 2015 | Lopez-Carpintero *et al.*[27] | 39 Multi gravida | Abortion | DNA | After medical treatment of abortion | Gestational vesicle with maximum anteroposterior diameter of 21 mm seen via ultrasound | No mass | 164 mIU/mL | DNA | Uterine vascular malformation | US: Heterogenous endometrium with maximum anteroposterior diameter of 21 mm, plenty of color map, reaching myometrium<br>CT: Uterine vascular malformation | Hysterectomy |

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**Table 3: Contd...**

| Published year | Authors | Age of patients/OB score | Type of (antecedent pregnancy) | Gestational age of (antecedent pregnancy) | When the lesion of clinical symptom was recognized | Clinical symptoms and features | Gross lesion | Initial beta HCG | Final beta HCG | Initial diagnosis | Imaging | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2015 | Shetty *et al.*[4] | 35<br>G5P2 | Abortion | 10–12th weeks | After curettage | Severe abdominal pain, fever, chills and vaginal bleeding | No mass | NM | NM | Septic abortion | NM | Curettage |
| 2015 | Kadian *et al.*[28] | 30<br>G3P2 | Preterm pregnancy | 36 weeks | After placental delivery | Uterine atony after placental delivery | No mass | NM | NM | Postpartum hemorrhage | US: Single live unanomalous fetus of 33±2 weeks AOG, anteriorly placenta in the upper segment and optimum amniotic fluid | Subtotal hysterectomy |
| 2016 | Jayakrishnan *et al.*[29] | 34<br>CS and abortion 1 | Missed abortion | Abortion 1 year ago | After hysteroscopy | Vaginal bleeding; diagnosed EPS based on pathology | With mass lesion seen during hysteroscopy | 6 mIU/mL | NM | GTD | US: Increased vascularity over the anterior and posterior myometrium suggestive of adenomyosis<br>Hysteroscopy: Fleshy mass seen on the posterior wall with increased vascularity seen over the fundus | Hysteroscopic resection |
| 2017 | Arora *et al.*[30] | 30<br>NM | Incomplete abortion | 14 weeks | After curettage | Vaginal bleeding, lower abdominal pain along with high fever | No mass | NM | NM | Incomplete abortion | NM | Curettage |
| 2017 | Ostwal *et al.*[31] | 45<br>Para 4<br>4 normal deliveries | Abortion, induced | 12 weeks | After curettage | Vaginal bleeding | Bulky adenomyotic mass | 15.68 mIU/mL | NM | Postabortion hemorrhage | US: Bulky uterus with heteroechoic vascular lesion in fundus and endometrium with likely invasion of the anterior myometrium (features favoring malignant etiology). CT scan confirmed increased vascularity in anterior myometrium and endometrium, suggestive of carcinoma uterus | Hysterectomy |

*Contd...*

**Table 3: Contd...**

| Published year | Authors | Age of patients/OB score | Type of (antecedent pregnancy) | Gestational age of (antecedent pregnancy) | When the lesion of clinical symptom was recognized | Clinical symptoms and features | Gross lesion | Initial beta HCG | Final beta HCG | Initial diagnosis | Imaging | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2018 | Sidhu *et al*.[32] | 30<br>G7P5<br>Abortion 2 | Normal pregnancy | Term pregnancy | After normal delivery | Severe uterine bleeding, EPS based on pathology | No mass | NM | NM | Postpartum hemorrhage | NM | Hysterectomy |
| 2020 | Sen *et al*.[33] | 35<br>G3P2 | Normal pregnancy | Term pregnancy | After CS | Vaginal bleeding | No mass | NM | NM | Postpartum hemorrhage | NM | Hysterectomy |
| 2020 | Yordanov *et al*.[34] | 44<br>G2P1 | Incomplete abortion | Abortion | After curettage | Prolonged vaginal bleeding | 3 cm ×3.5 cm tumor in the uterus | 332 g mIU/mL | 0.21 mIU/mL (3 months postoperation) | Submucous fibroid | US: Submucosal fibroid formation | Hysterectomy |
| 2021 | Pina *et al*.[35] | 15<br>G1P0 | Abortion | 11 weeks | Autopsy | Dyspnea, cardiac arrest | No mass | NM | NM | Pulmonary embolism | US: Intrauterine pregnancy with no cardiac activity | Died |
| 2021 | Pellegrino[36] | DNA | Abortion voluntary | Abortion | After vacuum aspiration | Massive vaginal bleeding after vacuum aspiration | No mass | DNA | DNA | Postabortion hemorrhage | DNA | Hysterectomy |

OB: Obstetric, NM: Not mentioned, GTD: Gestational trophoblastic disease, US: Ultrasonography, DNA: Data not accessible, AUB: Abnormal uterine bleeding, PSTT: Placental site trophoblastic tumor, MRI: Magnetic resonance imaging, EPS: Exaggerated placental site, CT: Cytotrophoblast, CS: Cesarean section, HCG: Human chorionic gonadotropin, NM: Not mentioned

Some characteristics of a neoplastic placental trophoblastic tumor were present in the index case's clinical, gross and microscopic presentation. Because PSTT tends to have a malignant course with disseminated metastases in 15%–30% of patients, it is an essential differential diagnosis that we need to rule out.[1] In comparison to a benign EPS lesion, its clinical course and treatment are very different.

As defined by the WHO, PSTT is a type of gestational trophoblastic neoplasia consisting of neoplastic implantation site-type IT.[8] A history that could span months to years following a term, abortion and molar pregnancy is a common clinical presentation of PSTT.[10] Serum beta HCG levels in PSTT might range from 0 to 58, 000 mIU/mL.[11] On gross examination, the endometrium is typically converted to a nodular, solid mass that range in size from 1 to 10 cm. Myometrial invasion is observed in 50% of the cases. Nearly half of the cases have focal bleeding and necrosis.[8] On histopathological evaluation, a monomorphic ISIT can be seen "splitting" the myometrium, which was also observed in the index case [Figures 5 and 6].

EPS, on the other hand, also shows extensive infiltration of the endometrium and myometrium by ISIT cells, many of which are multinucleated. Despite the massive infiltration by the trophoblastic cells, the overall architecture of the placental site is not disturbed. Endometrial glands and spiral arteries may be completely engulfed by trophoblastic cells, but there is no necrosis.[9]

To differentiate the two, PSTT exhibits variable mitosis of approximately 0-6/10 HPF,[9] while EPS has no mitotic activity. The presence of chorionic villi, which are linked to EPS, will essentially rule out the diagnosis of PSTT.[12]

In our index case, no mitotic activity was observed, and chorionic villi were visible under the microscope [Figure 9], indicating that this is a case of EPS. The uterine blood vessel wall was replaced with fibrinoid deposition with areas of hemorrhages and necrosis [Figures 7 and 8]. Necrosis and hemorrhages are usually present in PSTT and not seen in benign lesions such as EPS, but may be seen in the decidual vicinity in cases of spontaneous abortion. Other signs of pregnancy, such as hyalinized spiral arteries, hypersecretory glands, and chorionic villi, are usually present.[13]

Histopathological features alone are not sufficient to diagnose a rare gestational trophoblastic disease such as EPS. To assist in differential diagnosis, an algorithmic approach, termed "trophogram," using a three-tiered stepwise immunohistochemical staining procedure can be used.[9]

The first tier in the algorithm discriminates a trophoblastic versus a non-trophoblastic lesion by using HSD3B and LMW cytokeratin. These markers are diffusely positive and specific for trophoblastic origin.

**Table 4: Serum beta human chorionic gonadotropin**

| | Result (miU/mL) | Normal value (miU/mL) |
|---|---|---|
| On admission | 10,000 | 0.00–5.30 |
| 7th day postoperation | 177.6 | 0.00–5.30 |
| 3 weeks postoperation | 29.99 | 0.00–5.30 |

**Table 5: Thyroid function test**

| Test | Result | Normal Values |
|---|---|---|
| T4 | 8.07 | 5.10–14.10 µg/dL |
| T3 | 0.859 | 0.8–2 ng/mL |
| TSH | 0.711 | 0.47–4.64 uIU/mL |

TSH: Thyroid-stimulating hormone, T3: Triiodothyronine, T4: Thyroxine

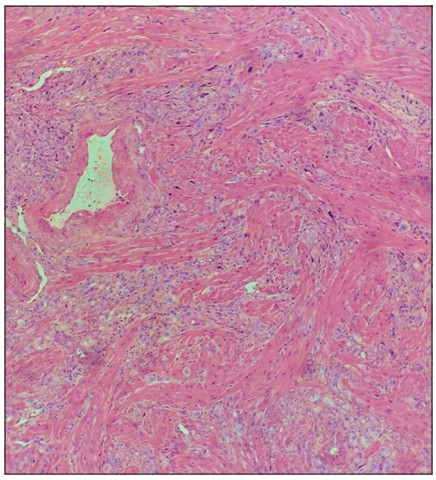


**Figure 5:** Histopathologic studies on low scanning view in hematoxylin-eosin staining. A diffuse and infiltrative growth of atypical monomorphic intermediate trophoblast arranged in sheets and cords are seen infiltrating the myometrial smooth muscle fibers

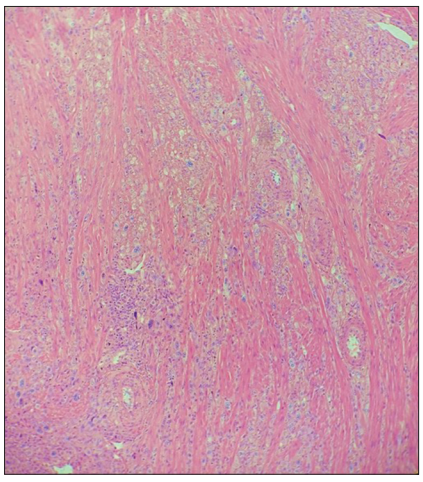


**Figure 6:** Intermediate trophoblast arranged in sheets and nests separating myometrial fibers ("splitting")

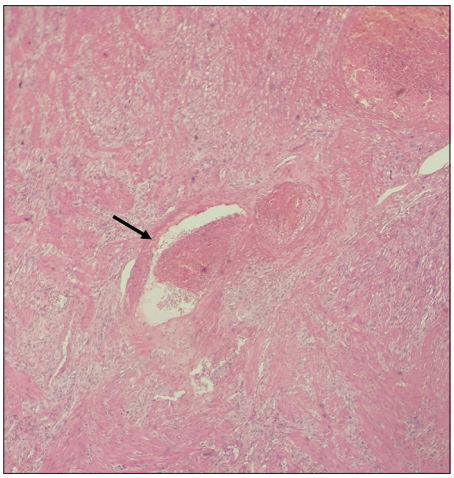


**Figure 7:** Uterine blood vessel wall replaced with extensive fibrinoid deposition (arrow)

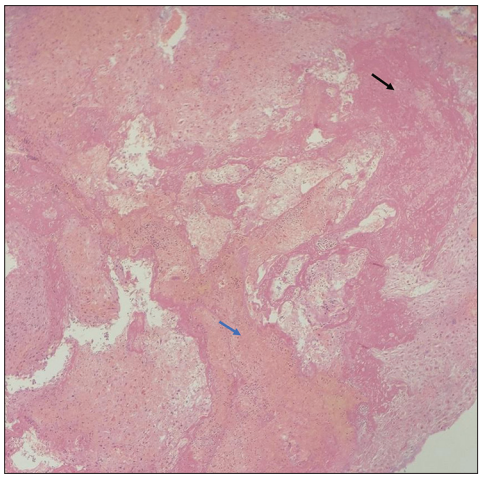


**Figure 8:** Areas of hemorrhages (blue arrow) and necrosis (black arrow)

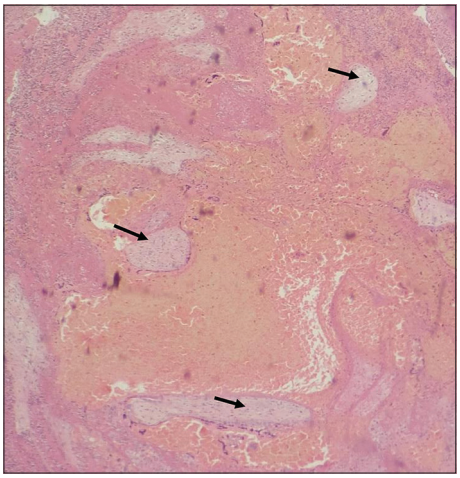


**Figure 9:** Presence of chorionic villi (black arrow)

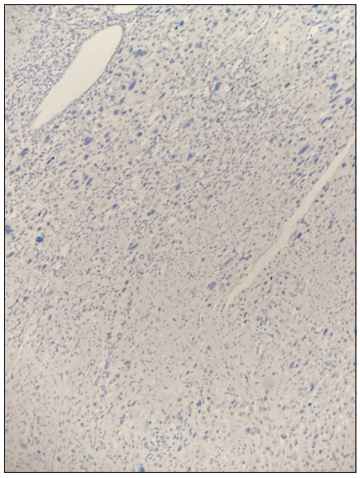


**Figure 10:** Ki-67 immunostaining is 0% showing no proliferation in the cells of interest

The second tier uses hPL and p63 markers to differentiate the ISIT from chorionic-type IT. hPL is diffusely positive in ISIT and can be positive or negative in chorionic type IT; p63 will be diffusely positive in chorionic type IT and negative in ISIT.

Finally, the third tier distinguishes a benign tumor-like lesion versus a trophoblastic neoplasm by using Ki-67 and cyclin E. Ki-67 immunostaining is used to differentiate EPS and PSTT. EPS will stain <1% for EPS and >10% in PSTT. Cyclin E and Ki-67 are used to differentiate PSN from ETT. In PSN, Ki-67 is <8% and cyclin E is negative, while ETT will show Ki-67 >12% with positive Cyclin E[9] [Figure 13].

Histopathologic studies in this case showed diffuse and infiltrative growth of atypical monomorphic ITs arranged in sheets and cords, infiltrating and separating myometrial fibers [Figures 5 and 6]. When we hear infiltrative growth with atypia, it can cause confusion because these are common characteristics of neoplasms. The infiltrative behavior of ISIT is needed to anchor the placenta.

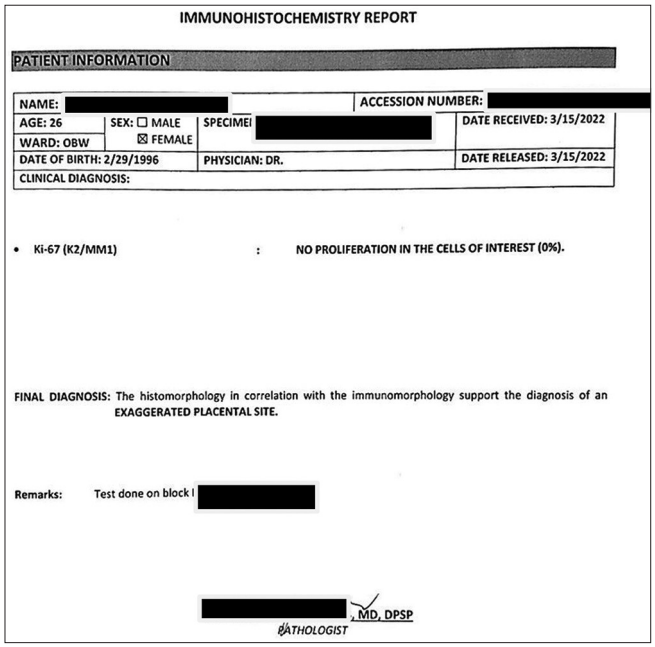
The clinical presentation, level of serum beta-hCG, and gross and microscopic findings of the index patient point to an EPS and PSTT diagnosis. The presence of chorionic villi [Figure 9] is rarely seen in PSTT; thus, the findings favored EPS rather than PSTT.

Lastly, to confirm the diagnosis, immunostaining of Ki-67 is required. Ki-67 expression is frequently used in standard pathological research as a proliferation marker since it is significantly associated with tumor cell proliferation and expansion [Figure 14]. An established prognostic and predictive marker for the evaluation of cancer patient biopsies is the nuclear protein Ki67.[14] A Ki-67 labeling index of <1% supports the diagnosis of EPS and >10% in PSTT.[9] The Ki-67 labeling index in our patient is 0 [Figure 10], confirming that this case is an EPS [Figure 11].

The histochemical immunostaining in the "trophogram" such as HSD3B and LMW, hPL, p63, and cyclin E, was not done because the clinical and morphological presentation of this case clearly points to intermediate implantation sites IT, EPS, and PSTT [Figure 15]. These immunohistochemical staining techniques are expensive and not available. Choosing the most needed immunostaining will help the patient save her resources.

The Ki-67 immunostaining was done to confirm the diagnosis. In our case, the Ki-67 immunostaining was 0%, showing no proliferation, supporting the diagnosis of an EPS.

The management of EPS will depend on the clinical profile of the patient and the desire to preserve fertility.



IMMUNOHISTOCHEMISTRY REPORT

PATIENT INFORMATION

NAME: [redacted] ACCESSION NUMBER: [redacted]

AGE: 26 | SEX: ☐ MALE ☒ FEMALE | SPECIMEI [redacted] | DATE RECEIVED: 3/15/2022

WARD: OBW | DATE OF BIRTH: 2/29/1996 | PHYSICIAN: DR. | DATE RELEASED: 3/15/2022

CLINICAL DIAGNOSIS:

- Ki-67 (K2/MM1) : NO PROLIFERATION IN THE CELLS OF INTEREST (0%).

FINAL DIAGNOSIS: The histomorphology in correlation with the immunomorphology support the diagnosis of an EXAGGERATED PLACENTAL SITE.

Remarks: Test done on block I [redacted]

[redacted], MD, DPSP
PATHOLOGIST

**Figure 11:** Final histopathology result

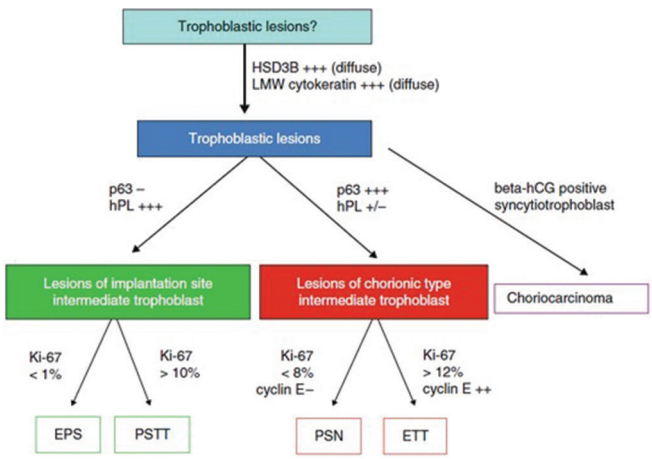


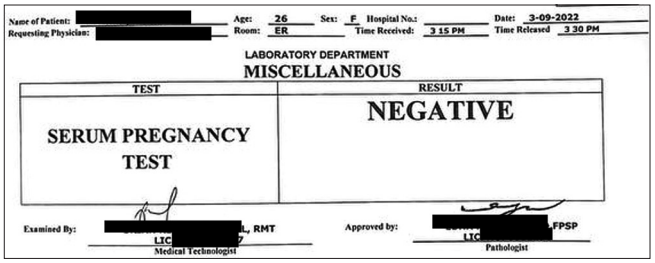

**Figure 13:** "Trophogram" showing the three-tiered stepwise immunohistochemical staining procedure.[9] EPS: Exaggerated placental site, PSTT: Placental site trophoblastic tumor, PSN: Placental site nodule, ETT: Epithelioid trophoblastic tumor, HCG: Human chorionic gonadotropin

The majority of patients in the review of related literature had hysterectomy procedures, two had curettage, two had resection, and two received methotrexate therapy. Nineteen were treated by hysterectomy to control severe uterine hemorrhage and prevent progressive GTD [Table 3]. Hysteroscopic resection or curettage can be done to preserve fertility. However, hysteroscopic resection may result in massive bleeding when vascular spaces like flow voids are detected by MRI.[15]

On the other hand, the conventional course of treatment for neoplastic trophoblastic tumors like PSTT in patients who present more than 4 years after the previous pregnancy is hysterectomy with adjuvant chemotherapy.[2] Because of the PSTT tumors' relative resistance to chemotherapy and propensity for lymphatic spread, hysterectomy with lymph node dissection is recommended.

In our index case, an emergency total abdominal hysterectomy was carried out due to severe uterine hemorrhage, multigravidity, no desire for future pregnancies and potential difficulty in adhering to serial postoperative surveillance.

Hysterectomy is not the best course of action for a young patient with EPS who presents with low beta HCG and does not have substantial uterine hemorrhage. Since EPS



Name of Patient: [redacted] Age: 26 Sex: F Hospital No.: Date: 3-09-2022
Requesting Physician: [redacted] Room: ER Time Received: 3 15 PM Time Released 3 30 PM

LABORATORY DEPARTMENT
MISCELLANEOUS

| TEST | RESULT |
|---|---|
| SERUM PREGNANCY TEST | NEGATIVE |

Examined By: [redacted], RMT
LIC
Medical Technologist

Approved by: [redacted], FPSP
LIC
Pathologist

**Figure 12:** Serum pregnancy test 8 weeks post operation

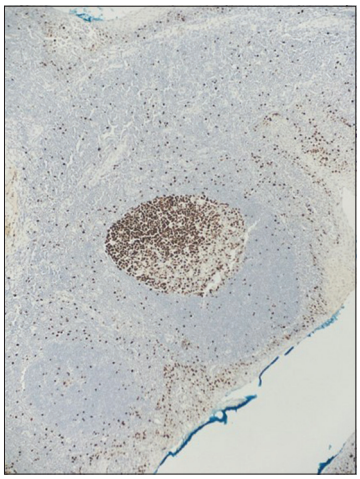


**Figure 14:** Picture showing the control. Proliferating cells labeled with paraffin-reactive antibody (against the Ki-67 antigen) are concentrated in the dark zone of the germinal center at the bottom away from the site of antigen entry from the tonsillar surface at top

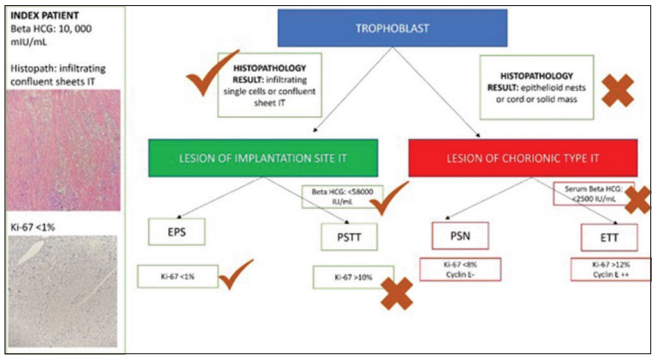



**Figure 15:** Diagnostic trophogram of index patient. EPS: Exaggerated placental site, PSTT: Placental site trophoblastic tumor, PSN: Placental site nodule, ETT: Epithelioid trophoblastic tumor, HCG: Human chorionic gonadotropin

is a completely benign condition which does not typically tend to develop into persistent GTD unless linked with a hydatidiform mole, a more cautious management strategy, such as curettage, can be used.

Serial Beta HCG surveillance following surgery is not required for EPS that is not accompanied by a hydatidiform mole because it does not pose an elevated risk of persistent GTD.[9] There were at least five case studies that mentioned undetectable or low levels of post-procedure Beta HCG (0.5 mIU/mL). No particular course of action or follow-up is necessary.

## Conclusion

Histologically, it is difficult to diagnose and differentiate GTD and neoplasia. It is important to have a complete history and physical examination in conjunction with diagnostic test such as serum Beta HCG and ultrasound. EPS is a benign trophoblastic lesion without any risk of persistent GTD, while PSTT is a type of gestational trophoblastic neoplasia and tends to have a malignant course with disseminated metastases. The distinction between EPS and PSTT and other GTNs is only made possible by histology and immunohistochemical tests. Documentation of future cases is required to build the body of evidence and establish criteria to diagnose these lesions with confidence based on morphology alone. However, the awareness of this rare entity is essential because the course of management and surveillance of non-neoplastic lesion such as EPS is remarkably different from neoplastic PSTT.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Authorship contributions

Marie Mae G. Pantolla-Laxamana, MD - involved in the conceptualization, investigation, writing- original draft, writing – review and editing, visualization, funding acquisition.

Merly R. Rosario-Reamillo, MD, FPOGS, MMHoA - involved in conceptualization, writing – review and editing, supervision.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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