Utility of ultrasound in monitoring gestational trophoblastic disease

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Learning objectives

Ultrasound is the imaging modality of choice for the diagnosis of Gestational Trophoblastic Disease. Accurate interpretation of US examinations of Uterus requires an understanding of the anatomy, pathophysiology and possible changes in the morphology, echogenicity and vascularity of the uterus and ovaries in both initial diagnosis and follow-up, an accurate diagnosis.

We propose to attend this goals

1. Recognize the different forms of sonographic presentation of trophoblastic disease.

2. Emphasize imaging features that can help a more accurate diagnosis during the follow-up after surgical treatment or pharmacological.
“UTILITY OF ULTRASOUND IN MONITORING GESTATIONAL TROPHOBLASTIC DISEASE”

National Cancer Institute
Mexico City

Fig. 1

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Background

Gestational trophoblastic disease (GTD) encompasses a spectrum of disease arising from uncontrolled growth of placental trophoblastic tissue, with a spectrum of severity ranging from premalignant hydatiform mole through malignant invasive mole, choriocarcinoma, placental-site trophoblastic tumor (PSTT) and the extremely rare epitheloid trophoblastic tumor. Early accurate diagnosis of GTD is necessary to avoid morbidity associated with delayed diagnosis from multidrug chemotherapy and surgery. Treatment is initiated once the imaging and clinical diagnosis is established. Follow up after evacuation of a hydatiform mole is essential to detect trophoblastic sequela (invasive mole or choriocarcinoma), which develop in approximately 15-20% with complete mole and 1-5% with partial mole.

1. INTRODUCTION

Hippocrates was probably the first to describe gestational trophoblastic disease around 400 BC, in his description of dropsy of the uterus. While other observations have been made since then, Marchand was the first to associate the hydatidiform mole pregnancy in the year de1895 (1).

Gestational Trophoblastic Disease (GTD) comprises a spectrum of diseases caused by an uncontrolled growth of placental trophoblast tissue, with a spectrum of severity ranging from mola premalignant to malignant mole invasive, choriocarcinoma, placental site trophoblastic tumor (PSTT) and extremely rare epithelioid trophoblastic tumor. Early and accurate diagnosis of the GTD is necessary to avoid the morbidity associated with delayed diagnosis; treatment is initiated once the imaging and clinical diagnosis have been established (2).

Transvaginal sonography has become an important method for evaluating shape, volume and blood flow of the uterus and ovaries. Color Doppler and pulsed has been widely used in the uterine vasculature, blood flow is evaluated by the pulsatility index (PI), resistance index (RI) and systolic and diastolic ratio (D:S) (3).

2. EPIDEMIOLOGY

Hydatidiform mole, is commonly known as a molar pregnancy, representing 80% of total Gestational trophoblastic disease. It is estimated to occur in 0.6 to 1.1 per 1000 pregnancies in the United States. Choriocarcinoma is rare, with an estimated 1 in
20,000 to 40,000 pregnancies incidence. Approximately 50% of choriocarcinoma arises from molar pregnancies, 25% of pregnancies at or near term and the remaining term pregnancies. Overall a significant decrease in the incidence of GTD in the past 3 decades, which in part can be attributed to improving socioeconomic conditions and changes in the diet.

Some of the established risk factors for GTD are maternal age (<20 years and >40 years), previous history of molar pregnancy and oral contraceptive use.

The risk of subsequent molar pregnancy is 1% to 2% after diagnosis of a molar pregnancy and 15% to 20% after diagnosis 2 molar pregnancies.

3. PATHOLOGY

Cytogenetic studies have shown that complete mole has a diploid karyotype and paternal origin. It is the result of fertilization of an empty ovum by a haploid sperm that duplicates its chromosomes; the karyotype zygote configuration with complete mole is 46XX. In about 4-20% of cases an empty ovum is fertilized by two sperm in 46XX resulting haploid or XY. In partial mole, a haploid ovum is fertilized by two sperm. The zygote therefore becomes triploid containing 69 XXY, XYY XXX rarely.

The complete mole is characterized by vesicles and thick villi although sometimes they cannot be present in early gestation. Histologically there are villi with central tank and a notorious trophoblastic proliferation. Cytotrophoblasts show a notorious cellular pleomorphism and no fetal tissues identified.

In contrast, thick hairs are occasionally found in partial mole and these tend to be smaller and fewer in number compared to the complete mole. Products of normal pregnancy as gestational sac, embryo, fetus or placenta may be present.

The villi with central tank and trophoblastic hyperplasia are less visible in partial mole and fetal tissues such as erythrocytes can be found. It can also identify serpentine aspect of the chorionic villi and trophoblastic inclusions.

P57 (KIP2) is a paternally printed gene and expressed by mother. The complete mole include parental DNA and absence of p57 (KIP2) identified in nuclear staining in trophoblasts and villous stroma cells.

By the way, since the partial mola and complete mola maternal containing DNA, p57 (KIP2) is positive; genotypically use variable number of tandem repeats, it can identify the paternal or maternal origin of polymorphic alleles; therefore it is possible to distinguish
the parental diploid or biparental diploidy and triploidy diandrogénica allowing non molar pregnancy diagnosis, partial or complete hydatidiform mole \(^{(4)}\).

4. FINDINGS OF IMAGE IN GESTATIONAL TROPHOBLASTIC DISEASE

4.1 Ultrasound

The gray scale ultrasound, Doppler color and Doppler spectral is a very useful diagnostic tool GTD, the presence of invasive disease predicts response in three important situations 1. Response to chemotherapy, 2. Monitoring post-chemotherapy and 3. Detection of disease recurrence.

4.1.1 Sonographic features of hydatidiform mole

Ultrasonography is the first imaging modality of choice for diagnosing clinical suspicion of hydatidiform mole, also in those with serum #hCG abnormally high (measured at the time of clinical presentation) and who can not be established a diagnosis of pregnancy.

Ultrasound can be done by transabdominal or transvaginal (TSV). Transvaginal ultrasound provides better detail of injury due to their superior spatial resolution and proximity to the anatomy of interest (Figure 2).

By the way, the transabdominal approach requires the patient to retain urine resulting in less discomfort and provides diagnostic information. Hydatidiform mole constitutes 80% of cases of GTD appearing more frequently as an enlarged uterus with endometrial mass (predominantly echogenic) heterogeneous echogenicity (Figure 3). The sonographic appearance classically described as "snowstorm" or "granular" it's secondary to multiple echogenic foci.

The transvaginal ultrasound shows higher resolution morphology of the lesion and/or presence of myometrial invasion (Figure 4).

The vesicles represent hydatidiform mole and the thickened villi are typically identified as multiple small anechoic spaces ranging in size from 1 to 30 mm, encountered during the first quarter (Figure 5-6).

With increasing gestational age, anechoic spaces become larger and more numerous due to the presence of prominent villi, so the ultrasound diagnosis of hydatidiform mole
is better identified in the second quarter than in the first trimester of pregnancy, even by transabdominal approach. Uterine volume must also be accurately estimated by ultrasound as it correlates with tumor burden and thus determines the risk of invasion.

A fetus or fetal parts are not in a complete hydatidiform mole except in 1-2% of cases with the coexistence of dizygotic twin pregnancy. Otherwise, the partial mole is usually associated with an abnormal fetus and placenta delay thickened and numerous large anechoic cystic lesions. Differentiation of complete and partial moles can be difficult, but is of limited clinical importance because the treatment is similar.

Although ultrasound is useful to suggest a molar pregnancy, the final diagnosis remains with the histopathologic findings.

The finding of a heterogeneous endometrial mass is nonspecific and can also be seen in the retained products of conception, hemorrhage or hematoma (Figure 7-8). Sometimes it may seem like a collection of large liquid, central, mimicking pregnancy anembryonic or miscarriage. However, the correlation with clinical features and h-hCG is useful in making the differentiation.

The ovaries may show a secondary tecaluteínico cyst hyperstimulation by high levels of gonadotropin; this finding is present in up to 40% of cases. Multiloculated and cysts are usually bilateral (Figure 9). Rarely they can occur secondary hemorrhage ruptures producing an acute abdomen. Usually resolve within a few months after treatment.

4.1.2 Sonographic features of invasive disease

The myometrial invasion it best seen in transvaginal scan due to differentiation of the interface between the trophoblastic tissue and myometrium. The invasive mole, choriocarcinoma and placental site trophoblastic tumors are best identified grayscale as focal masses in the central area of the myometrium, which may be multiple unable to distinguish one from another.

The dough may be echogenic, hypoechoic, or multicystic complex. Us can show anechoic spaces representing hemorrhage, necrosis, cysts or vascular spaces. The more extensive disease may appear as a heterogeneous uterus increased in size lobed contours or large pelvic mass that may involve other organs in the pelvis. These masses can potentially be mistaken for fibroids and adenomyosis.

The adenomyosis typically appears as a diffuse disease process causing an enlarged uterus with heterogeneous diffuse texture. It can also manifest as asymmetrical thickening of myometrium, myometrial cysts, endometrial-myometrium interface.
indistinct, polyploid injury, or focal mass within the myometrium with poorly defined margins that blend with the surrounding myometrium.

The fibroids usually occur typically as a well-circumscribed hypoechoic lesion myometrium, although echogenicity may vary. The various presentations ultrasound gestational trophoblastic neoplasia may be confused with these imaging findings of fibroids and adenomyosis. However, the correlation with serum #-GHC, medical history and lack of important vascularization at color Doppler, help for identification\(^{(5)}\).

### 4.1.3. Doppler's Role.

The color and spectral Doppler routinely performed well grayscale for the diagnosis of primary or recurrent GTD after treatment and monitoring. In a normal pregnancy in the first trimester intrauterine arteries flows show high strength low diastolic velocity, except in the area of implementation. It reduces the flow resistance in the second and third trimester, with increased physiological blood invasion by trophoblast tissue.

In contrast, molar pregnancy shows a high speed, the waveforms of low impedance in the first quarter and early in the second, due to the high degree of arterial invasion by the abnormal proliferation of the trophoblast (Figure 10).

The arteriovenous shunts are associated with secondary neovascularization to the myometrial invasion with an aspect of vascular turbulence and color aliasing and loss of vascular morphology linear images in the color Doppler (Figure 11 and 12); this extreme vascularity appears as high speed and low flow impedance. The vascular impedance can be quantified using ratios derived from the waveform of the uterine artery pulsatility index known as (IP) and the resistance index (RI).

These characteristics of Doppler ultrasound can also be viewed from any cause of increased pelvic blood flow such as: retained products of conception, ectopic pregnancy, pelvic inflammatory disease, malignant tumors of non-trophoblastic pelvis, uterine arterio-venous malformation. Zhou et al they observed lower rates of resistance (IR) in invasive mole and choriocarcinoma as well as partial or complete, indicative of a greater degree of vascular invasion in the first two\(^{(5)}\).

### 5. MAGNETIC RESONANCE IN GESTATIONAL TROPHOBLASTIC DISEASE
The MRI has a role in the routine evaluation of the TGD and usually is used as a tool of exclusion or in difficult cases. On pelvic MRI, hydatidiform mole usually appears as a flagrantly hyperintense heterogeneous mass distending the endometrial cavity in T2-weighted images. On T1-weighted images with contrast, especially during the second quarter, small cystic spaces show a diffuse distribution within the solid lesion and surrounding normal myometrium it (Figure 16). The tecaluteínicos cysts can be observed in some cases.

The invasive moles and choriocarcinoma are usually seen with loss of the interface of the endometrium / myometrium weighted sequences both in T1 and T2 with a heterogeneous appearance. This heterogeneous appearance may be partly due to tumor necrosis or hemorrhage. The extent of extrauterine disease in the parametrium or vagina can be better evaluated with the MRI to ultrasound. Other findings are loss of normal anatomy although this may be a nonspecific finding and may be present in other conditions such as incomplete or history of recent curettage abortion.

The two types of placental site trophoblastic tumors may differ in appearance, the type hipervascular may appear as a T1 isointense and slightly hyperintense on T2, with significant enhancement of vascular structures.

The hypovascular type can be hyperintense normal myometrium both T1 and T2 with some areas showing enhancement after administration of contrast may be no secondary signal to a prominent vascularity.

The brain scan may be performed to rule out metastatic disease in patients with persistent trophoblastic neoplasia (Figure 15). The signal characteristics of these metastases are often hemorrhagic (5).

6. POSITRON EMISSION TOMOGRAPHY ON PERSISTENT TROPHOBLASTIC DISEASE

There are limited data on the efficacy of PET / CT in the evaluation of patients with gestational trophoblastic neoplasia data. The marker 18-FDG has the potential to identify patients with occult disease recurrence or metastasis.

In staging the ETG, PET is not able to show relevant information in patients with low risk of FIGO classification, while in patients with high-risk disease may be helpful in identifying sites metastatic disease.
In patients with beta-hCG detectable persistent after chemotherapy, PET / CT can provide adequate treatment, particularly in patients in whom a single site of metastatic disease (Figure 13 and 14), surgical treatment is detected radical should always be considered especially in women who have been treated with multiple lines of chemotherapy (6).
Fig. 2: Figure 2. US TSV, gray scale. Uterus increased in size with the largest presence of multiple cystic areas up to 20 mm (arrow) in a 25 year old woman with high levels of β-GHC. No gestational sac is identified. References: Radiology department, National Cancer Institute-Mexico City

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Figure 3. Suprapubic gray scale US. Uterus with mass presence of mixed aspect, identifying cystic areas and other echogenic, not endometrial interface is observed. References: Radiology department, National Cancer Institute-Mexico City.

Fig. 3: Figure 3. Suprapubic gray scale US. Uterus with mass presence of mixed aspect, identifying cystic areas and other echogenic, not endometrial interface is observed. References: Radiology department, National Cancer Institute-Mexico City.

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Fig. 4: Figure 4. US Transvaginal. Uterus with echogenic mass presence with multiple cystic areas which shown myometrial invasion, findings of a complete mole. References: Radiology department, National Cancer Institute-Mexico City

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Fig. 5: Figure 5. Uterus with presence of heterogeneous echogenic mass with cystic areas up to 25 mm (arrow) in a patient of 23 years old. In the sagittal cuts important saturation color doppler vascular (dotted arrow) is identified. Findings of invasive mole. References: Radiology department, National Cancer Institute-Mexico City.
Fig. 6: Figure 6. Retroverted uterus showing prominent cystic areas (arrows) features complete mole in a patient of 31 years and $\beta$ -hCG levels of 254 IU / l. References: Radiology department, National Cancer Institute-Mexico City

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**Fig. 7:** Myometrial, residual, partially calcified hematoma that moves and compresses the complex a patient of 26 years with treatment (curettage) of GTD.

References: Radiology department, National Cancer Institute-Mexico City

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Fig. 8: Follow up at three months, case figure 6. HGC 4 UI

References: Radiology department, National Cancer Institute-Mexico City

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**Fig. 9:** Figure 9. Female 31 years old diagnosed with complete mole, tecaluteínicos cysts in both ovaries are observed with $\beta$ -hCG levels of 254 IU/l. References: Radiology department, National Cancer Institute-Mexico City

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Fig. 10: Figure 10. Uterus in axial section showing the increase in saturation color Doppler (Table A), the spectral Doppler (Table B) wave morphology is low impedance and high speed and low resistance index of 0.5 References: Radiology department, National Cancer Institute-Mexico City

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**Fig. 11:** Figure 11. Uterus with echogenic areas and multiple cystic images (picture b) the application of color Doppler displays important saturation and "mosaic" aspect (arrow) that translate in arteriovenous shunts, characteristic of complete mole. References: Radiology department, National Cancer Institute-Mexico City

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Fig. 12: Figure 12. Uterus in axial section, having increased color saturation the prominent vascular doppler paths (Table A), the spectral Doppler waveform morphology shown low impedance and high speeds of up to 50 cm / sec (Table B). References: Radiology department, National Cancer Institute-Mexico City

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Fig. 13: Female 19 years old with a history of invasive mole hysterectomy, the vaginal canal is shown with increase in thickness and with heterogeneous echogenicity (arrow). References: Radiology department, National Cancer Institute-Mexico City

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**Fig. 14**: Figure 14. Previous patient. The PET-CT shown a hyper metabolic focal zone without tomography translation with 3.4 SUV_{max}. References: Radiology department, National Cancer Institute-Mexico City

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**Fig. 15:** MRI skull. Patient tracking by invasive mole. Axial sequences (Tables A, C and D) no metastatic lesions, no reinforcements to the administration of gadolinium (Table B) References: Radiology department, National Cancer Institute-Mexico City

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Fig. 16: Figure 16. MRI of Pelvis. A Female of 18 years old in follow up to GTD with elevation β - hCG. The myometrium showing heterogeneous enhancement in the previous wall (A-B) in a Uterus didelphic (C). References: Radiology department, National Cancer Institute-Mexico City

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Findings and procedure details

In some cases the evaluation was conducted annually, at two and four years. The study sample was from 2011-2015.

The sonographic examination included evaluation sagittal and coronal grayscale, color Doppler and pulsed Doppler.

The age of the patients was from 15-34 years old.

The sonographic evaluation was performed with the Alpha 7 Aloka Ultrasound premier using the endocavity transducer (UST-670P) with a frequency range of 3-7.5 MHz.

From April 2011 to September 2015, 10 patients were evaluated at the National Institute Cancer of Mexico City for gestational trophoblastic disease. Among these 7 patients (70%) had a complete hydatiform mole, 1 patient (10%) developed endometrial hematoma and two patients (20%) developed partial hydatiform mole.

At follow-up 30% of the patients presented a heterogeneous utero followed by 10% of focal hypoechoic areas and 10% echogenic nodular areas, these latter related to disease recurrence.
### Table 1

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<td>RECURRENCE AFTER TWO YEARS</td>
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<tr>
<td>B</td>
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<tr>
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# Table 2

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**FOLLOW - UP**

**Figure 17.** Initial ultrasound, month, year and two years transvaginal ultrasound gray scale. A female of 18 years old in follow up to GTD, showing s: Radiology department, National Cancer Institute-Mexico City

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**Fig. 18**: Figure 18. Initial ultrasound, month, year and two years transvaginal ultrasound gray scale. ill-defined hypoechoic areas and other echogenic (arrow). A female of 18 years old in follow up to GTD. Radiology department, National Cancer Institute-Mexico City

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Conclusion

Compared with grayscale images, color Doppler produces a focal change in "honeycomb" which occurs early, also identifies the depth of the lesion which is useful for clinical monitoring of GTD.

The sonographic evaluation in disease recurrence is extremely important, considering that echogenic or increased vascularity at color Doppler focal areas are signs to be identified.
Personal information

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References