6 Imaging in Gestational Trophoblastic Disease and Implication of Uterine Artery Doppler Study

Goldwin H. Cecil, Anuradha Chandramohan, and Abraham Peedicayil

6.1 Introduction

Gestational trophoblastic disease (GTD) includes a broad spectrum of clinical diseases that arise from placental tissue and range from benign to malignant conditions. Around 15–20% of complete hydatidiform moles (CHM) and 0.5% of partial hydatidiform moles (PHM) advance to invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). The latter are collectively called gestational trophoblastic neoplasms (GTN) [1]. Early clinical suspicion and accurate diagnosis will have a great impact on reducing the morbidity in these patients. Though most of the persistent trophoblastic diseases follow benign hydatidiform moles, GTN can also occur after miscarriages, ectopic pregnancies, and even normal pregnancies. Prompt diagnosis will preserve fertility, reduce the use of chemotherapy, and improve outcomes. The role of imaging in the management of gestational trophoblastic diseases is crucial to accomplish this goal.

There are geographic variations in the incidence of GTD with the highest incidence reported in South East Asia [2]. Although there may be true variations in incidence, some of the variability may be due to differences in how the numerator and the denominator are arrived at. The predisposing factors for the increased incidence include the extremes of ages, i.e., <20 years and > 40 years and previous molar pregnancy [3]. GTN is known to arise from CHM, PHM, miscarriages, or even term delivery. The incidence of choriocarcinoma after a term delivery is 1/50,000 [4].

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B. Nayak, U. Singh (eds.), *Gestational Trophoblastic Disease*,
https://doi.org/10.1007/978-981-33-4878-3_6

Vaginal bleeding in early pregnancy should raise the suspicion of a molar pregnancy apart from ectopic pregnancy and some form of abortion. Along with clinical examination, quantitative assessment of the β-hCG levels and ultrasonography play a valuable role in the early diagnosis of a hydatidiform mole. Color Doppler study and subsequent follow-up of hCG values will help in diagnosing post-molar sequelae. CT of the chest abdomen and pelvis and MRI of the pelvis and brain have vital roles in the accurate staging and prognostication of GTN, the diagnosis of which is made mainly on the basis of rise or plateau of serum hCG values.

6.2 Pathology

Almost 95% of CHM have a 46 XX karyotype when an abnormal ovum devoid of maternal chromosomes is fertilized by one or more haploid sperm in an attempt at parthenogenesis. If a single sperm is involved, the paternal chromosomes duplicate to establish a diploid karyotype. The gross specimen has an appearance like a bunch of grapes, due to edematous villi formed from cytotrophoblasts and syncytiotrophoblasts [5].

Majority of PHMs are triploid karyotypes when a single haploid ovum is fertilized by two sperms. In PHM, there is less villous edema and there is usually an abnormal embryo that rarely survives beyond the second trimester. Diagnosis of PHM is often missed since the uterine size may be near normal, imaging findings are usually subtle and the β-hCG levels may not be significantly increased. Molecular genotyping using either polymorphic STR analysis or alternatively analysis by whole genome SNP microarray can be used to differentiate a CHM from a PHM and non-molar abortions.

Persistent elevation of β-hCG values after evacuation of a CHM or a PHM is the hallmark of GTN. Invasive mole is characterized by varying degrees of myometrial invasion. Choriocarcinoma is the most aggressive form of GTN and has necrotic and hemorrhagic components. Histologically, choriocarcinomas resemble an implanting blastocyst with no formed chorionic villi. Presentation can be varied and can even present years after conception or may occur de novo in the uterus. It is angio-invasive and hematogenous hypervascular metastasis most commonly to lungs, liver, brain, and vagina [6].

Placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) are rare forms of GTN, which share many similarities. They arise in the placental implantation site from the intermediate trophoblasts in young women of reproductive age group following a pregnancy. Both these tumors occur more commonly following normal delivery, yet can occur following CHM, PHM, and miscarriages. They are slow-growing tumors with propensity for local invasion and lymph node metastases [7]. Serum hCG levels are not very high in these patients and they respond poorly to chemotherapy. Thus, surgery remains the main treatment of choice [8].

Table 6.1 FIGO staging (2006) of gestational trophoblastic neoplasms

Stage	Tumor extent
Stage I	Tumor confined to the uterus
Stage II	Tumor extends beyond the uterus, limited to the genital structures
Stage III	Tumor extends to the lungs, with or without known genital tract involvement
Stage IV	Tumor involves all other metastatic sites

Table 6.2 Revised FIGO prognostic scoring 2006

FIGO score	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from the index pregnancy	<4 months	4–6 months	6–12 months	>1 year
Pretreatment hCG (mIU/ml)	<1000	1000–10,000	10,000- 1,00,000	>1,00,000
Largest tumor size including uterus (cm)	<3	3–5	>5	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Brain, liver
Number of metastasis	–	1–4	5–8	>8
Previously failed chemotherapy	–	–	Single drug	Two or more drugs

(Prognostic scoring for GTN based on clinical features, total serum β-hCG, and chest X-ray)

6.3 Staging

The FIGO staging is an anatomical one that does not correlate very well with biological behavior and prognosis. The WHO/FIGO prognostic scoring system should be used along with the anatomical staging to make management decisions. These are given in Tables 6.1 and 6.2.

6.4 Role of Imaging in the Management of GTD

Ultrasonography and color Doppler study are the imaging modalities of choice in the initial evaluation and diagnosis of GTD. Cross-sectional imaging methods such as contrast-enhanced CT, MRI, and PET-CT have important roles in the staging and surveillance of patients with GTNGTN. These tests can be ordered when specific indications arise and is going to decide the management protocol.

6.5 Ultrasonography

Ultrasound of pelvis is the first radiological investigation of choice in the evaluation of women with vaginal bleeding during pregnancy. One cannot emphasize the role of ultrasound and doppler in the diagnosis of GTD. With improved imaging, diagnosis is now made much earlier than in the past.

The most common finding in a woman with CHM is an enlarged uterus with echogenic endometrial contents [9]. Though missed abortion may have similar findings, presence of elevated β-hCG must raise suspicion of CHM. The characteristic image of a CHM on ultrasound is the "snow-storm" in A-mode or "honeycomb" or "cluster of grapes" appearance in B-mode. Higher resolution of transvaginal ultrasound will allow better visualization of the interface between the uterine myometrium and the trophoblastic tissue and helps with identifying myometrial invasion. Multiple anechoic vesicles of varying sizes (ranging between 1 and 30 mm) formed from hydropic chorionic villi give the typical appearance (Figs. 6.1 and 6.2) on

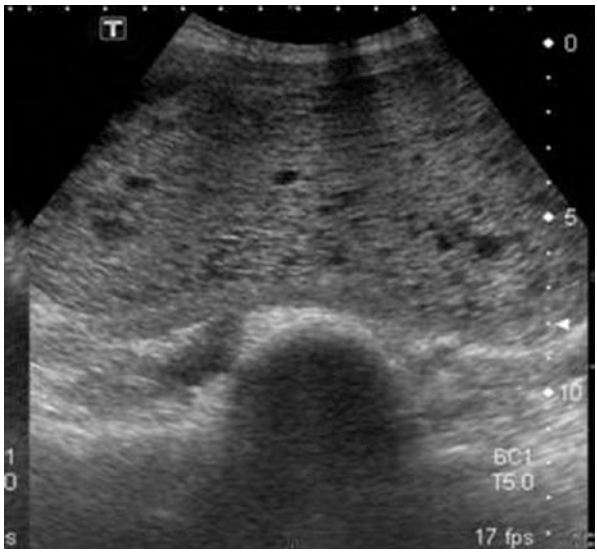

Fig. 6.1 Ultrasound image of the complete hydatiform mole showing echogenic mass and multiple cystic spaces in an enlarged uterus

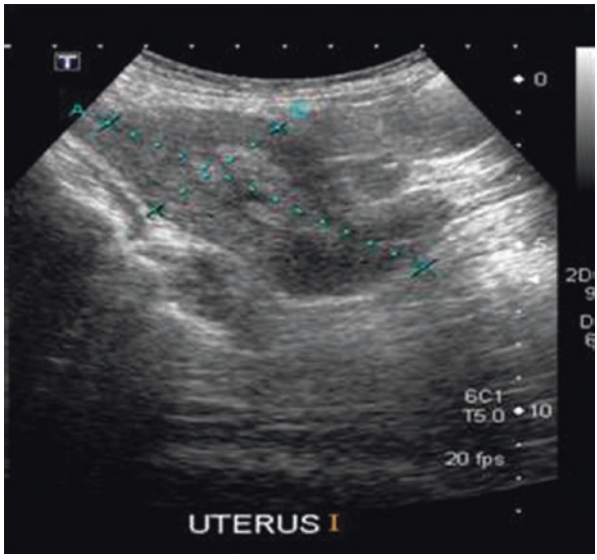

Fig. 6.2 Ultrasonography of a patient with invasive mole showing invasion into the anterior myometrium where there is loss of smooth interface between the echogenic mass and the myometrium

B-mode ultrasound [10]. In addition, large irregular cystic spaces from cystic degeneration may be seen within the endometrial mass. These findings become obvious even in the transabdominal ultrasound by the second trimester due to large uterine size and increase in the size and the number of the vesicles. Confirmation of myometrial invasion or excluding the same is crucial prior to suction evacuation of the uterus since the invasive component cannot be removed with evacuation [11] and these patients are likely to have persistent disease. Fetal parts or the fetus is typically absent in CHM unless rarely when CHM coexists with a diploid twin. About 20% of CHM have theca lutein cysts from ovarian hyperstimulation [12].

In PHM, there is thickened placenta with anechoic cystic spaces much fewer in number when compared to CHM [13]. This is usually associated with the presence of oval gestational sac, amniotic membrane, and a nonviable or incompletely formed embryo [14]. Naumoff et al. established criteria for diagnosing PHM stating that the placenta should be enlarged with numerous anechoic spaces, with a gestational sac and retarded growth of the fetus [15].

Table 6.3 summarizes the ultrasound imaging features of CHM and PHM. Differentiating CHM from PHM has prognostic significance due to the

Table 6.3 Ultrasound and Doppler features of CHM, PHM, incomplete abortion, and GTN

Feature	CHM	PHM	Incomplete abortion	GTN
Uterine size	Larger than appropriate for dates	Smaller than appropriate for dates	Smaller than appropriate for dates	Variable, usually enlarged uterus
Placental size	Normal	Enlarged and thickened	Normal	Absent
Placental architecture	Normal	Multiple anechoic cysts in the placenta	Normal	Absent
Fetal tissue	Absent	Present, usually non-viable	Present, non-viability is a rule	Absent
USG pattern	Snowstorm appearance	Swiss cheese appearance	Hyperechoic contents in the endometrial cavity	Heterogeneous echogenic mass. Loss of endometrium myometrium interface
Theca lutein cysts	Common	Less common	Rare	Common
Doppler color flow	Increased uterine vasculature, limited to the cystic vascular spaces in the endometrium	Increased uterine vasculature, limited to the cystic vascular spaces in the endometrium	Multiple feeding vessels around the hyperechoic contents	Increased vasculature with abnormal arteriovenous malformations. Vascular spaces extend into the myometrium
Resistivity index (RI)	Lower limit of normal (0.55)	Lower limit of normal (0.55)	Normal (0.66)	Low resistance flow (0.28)

differences in the rates of developing GTN in these conditions. While 15–20% of CHM progress to GTN, only 0.5% of PHM develop GTN. Though the differences between the ultrasound findings between these two entities have been well described, less than 50% of GTD are detected on routine ultrasound with obviously better detection rates for CHM (58–95%) when compared to PHM (17–29%) [16–18]. The overall sensitivity, specificity, PPV, and NPV of ultrasound for diagnosing any form of gestational trophoblastic disease is 44, 77, 88, and 23%, respectively [16]. Thus, the need for histopathological analysis of the products of conception of all nonviable pregnancies becomes essential.

The purpose of ultrasound in patients with clinically suspected GTN due to persistently elevated β-hCG following suction evacuation of molar pregnancy is to exclude normal intrauterine pregnancy, to measure the size of the mass and the uterus and, to assess the extent of local spread of disease [19]. The imaging features of GTN are by themselves nonspecific and may appear as hypoechoic or hyperechoic heterogeneous endometrial mass due to hemorrhage and necrosis. Following the diagnosis of GTD, ultrasound of the whole abdomen in GTN is usually the initial imaging procedure.

6.6 Color Doppler Study

Color Doppler study has the capability of noninvasively demonstrating the same findings as the pelvic arteriogram and has been shown to be of value in the management of GTN.

6.6.1 Doppler in Differentiating CHM and PHM

In clinical practice, uterine artery Doppler indices cannot be used to differentiate between CHM and PHM. However, Doppler indices are useful for identifying CHM coexisting with a normal fetus. Uterine artery RI (UA-RI) in normal pregnancy is significantly higher (mean RI = 0.66 ± 0.05) than the UA-RI in CHM (mean RI = 0.56 ± 0.04) and PHM (mean RI = 0.55 ± 0.06) [20].

6.6.2 Doppler in the Prediction of GTN and Chemoresistance

Color Doppler studies have potential roles in the prediction of GTN both before and following the evacuation of molar pregnancy. Lower UA Doppler indices were associated with the development of GTN (mean Resistive Index (RI) = 0.29) when compared to those who had spontaneous remission (mean RI = 0.46) [21, 22]. Presence of myometrial and endometrial nodules or masses showing hypervascularity 3 weeks after evacuation of the molar pregnancy highly correlated with the development of GTN. However, they are late findings. Doppler flow velocimetry can potentially identify disease early much before ultrasound findings can be seen.

While the negative predictive value of a normal Doppler study was 100% for development of GTN, the positive predictive value of abnormal Doppler findings 6 weeks following evacuation was 67% for residual local disease [24]. Of all the Doppler indices, Pulsatility Index (PI) was found to have the strongest predictor of developing GTN pre and post evacuation of CHM. PI is a parameter that assesses the pulsatility of the blood flow and it is given as the difference between the maximum and minimal flow velocity normalized to the time-averaged velocity. The formula for calculating PI is (peak systolic velocity (PSV)—end diastolic velocity (EDV))/time-averaged velocity (TAV). On the other hand resistive index (RI) is a measure of resistance to blood flow caused by microvascular bed, which is distal to the index vessel. The formula for calculated RI is (PSV—EDV)/PSV.

A PI value of </=1.3 pre-evacuation predicted the development of GTN with 77% sensitivity and 87% specificity. A cutoff value of PI</=1.7 post evacuation predicted the development of GTN with 79% sensitivity and 86% specificity [23]. PI < 1.1 is associated with chemoresistance to methotrexate and such low PI is an indirect evidence of increased tumor neovascularization and arteriovenous shunting [24].

In summary, uterine artery Doppler indices significantly increase in patients with spontaneous remission of molar pregnancy while they remained low in patients who are at risk of developing GTN. PI is the most useful parameter available to study the risk of developing GTN pre and post evaluation of molar pregnancy. Low PI value of <1.1 can predict resistance to methotrexate.

Figure 6.3 shows the Ultrasound—Color Doppler appearance of choriocarcinoma and the high-velocity low-resistance flow in the tumor vessels. Also demonstrated are the right and left uterine artery velocimetry values and spectral trace in these vessels.

6.7 Computed Tomography and MRI

CT has little role in the primary diagnosis of GTN. When identified CT can show a hypervascular uterine mass in patients with choriocarcinoma (Fig. 6.4) with parametrial infiltration (Fig. 6.5). Contrast-enhanced CT of the thorax, abdomen, and pelvis is useful for staging of proven GTN.

FIGO recommends plain chest radiograph for evaluation of metastases to the lungs. The importance of solitary metastases is yet to be analyzed completely. The clinical outcomes related to the number of metastases are also not clear. But it is common for CT to detect more lesions in the lungs compared to plain chest radiographs. However, small lesions seen only on CT are not used in the prognostic scoring. CT thorax can be advised if patient is symptomatic to rule out pulmonary thromboembolism. In high-risk patients, a CT thorax is recommended as plain film does not pick up about 41% of the lung metastases (Fig. 6.6). Liver metastases occur much later in the disease process and have poor prognosis. Liver metastases are hypervascular and these lesions should not be biopsied due to risk of life-threatening hemorrhage.

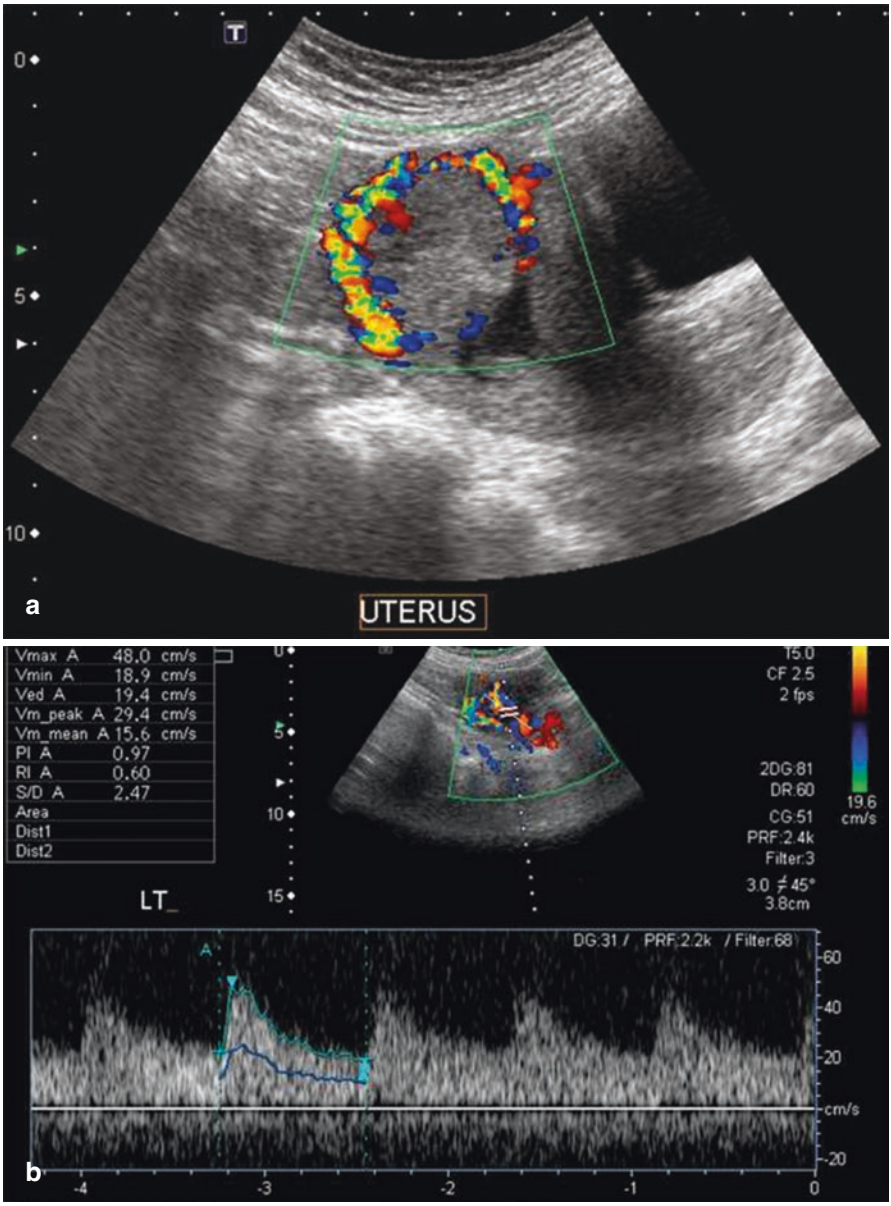

Fig. 6.3 Color Doppler image (**a**) and Doppler flow velocimetry in choriocarcinoma in the left uterine artery (**b**). Notice the low pulsatility index (PI) and resistive index (RI)

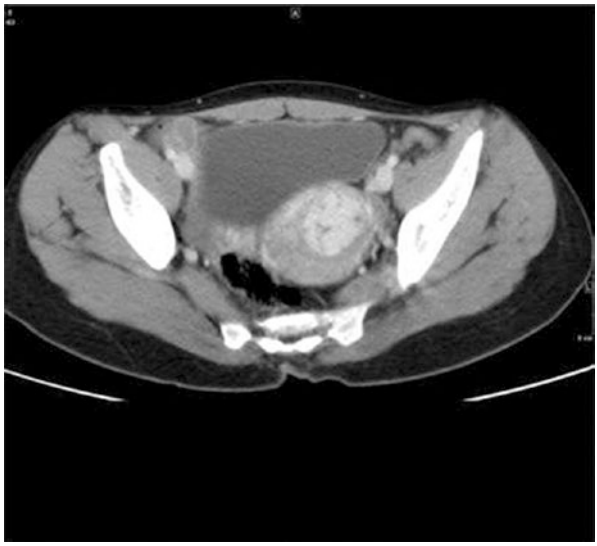

Fig. 6.4 CT abdomen showing enhancing mass in the uterus with possible myometrial invasion

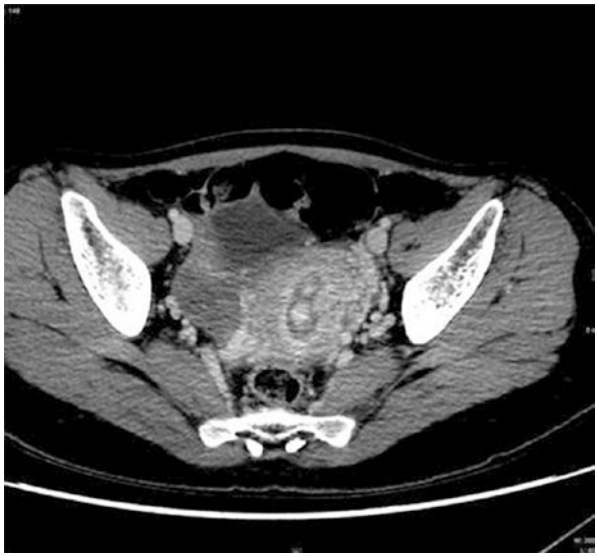

Fig. 6.5 CT Abdomen images of a patient with choriocarcinoma showing extension into the parametrium with the avid enhancement of the tumor

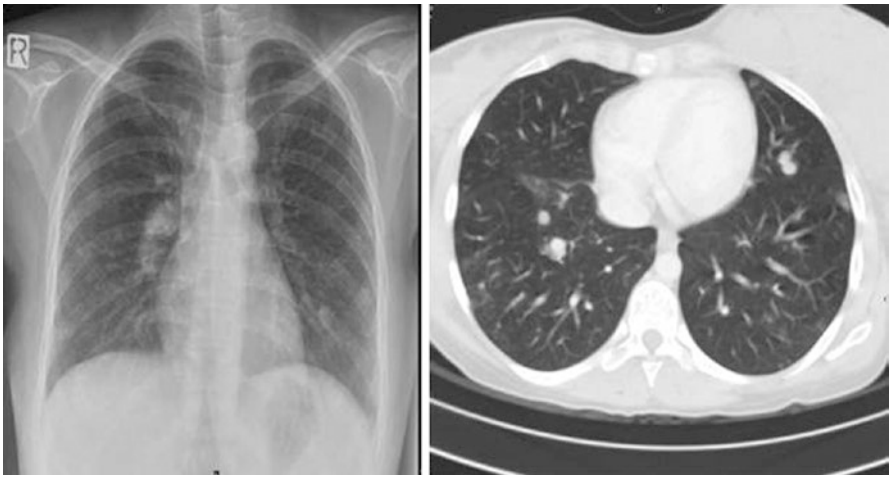

Fig. 6.6 Plain chest radiograph and CT thorax in lung window of a patient with choriocarcinoma showing multiple pulmonary metastases on CT

Central nervous system involvement has been noted in ~15% of the patients with metastatic disease. Patients with lung metastases are at increased risk of CNS spread. MRI of the brain is the investigation of choice for diagnosing brain metastases and for their follow up. Also, 85% of brain metastases occur in non-molar choriocarcinomas who have 20% risk of brain metastases. Thus, the importance of routinely imaging the brain in these patients [25]. On the other hand, the prevalence of brain metastases is extremely low in patients with post-molar choriocarcinomas.

MRI pelvis has a role in the local staging of disease in the pelvis. Metastases to the vagina are due to direct extension of primary uterine lesion and can occur in 30% of patients. MRI pelvis is the investigation of choice for these patients. Other regions involving metastases from GTD include the kidney, gastrointestinal tract, and the skin [26].

6.8 Digital Angiography and Intervention

Arteriovenous malformations (AVM) are a part of the normal pathogenesis of gestational trophoblastic neoplasms where there is direct communication between the arteries and the veins without an intervening capillary bed. Though most of them resolve after treatment for GTD, 10–15% of AVMs tend to persist even after a complete cure of GTD. Of these AVMs only ~2% of them may require treatment due to refractory vaginal bleeding [27, 28].

Color Doppler studies can be used for identifying AVMs, flow aneurysms, and arterio-venous fistulas, which show high-velocity low-resistance flow patterns with severe aliasing (misidentification of signals; see Fig. 6.7). Angiography shows a

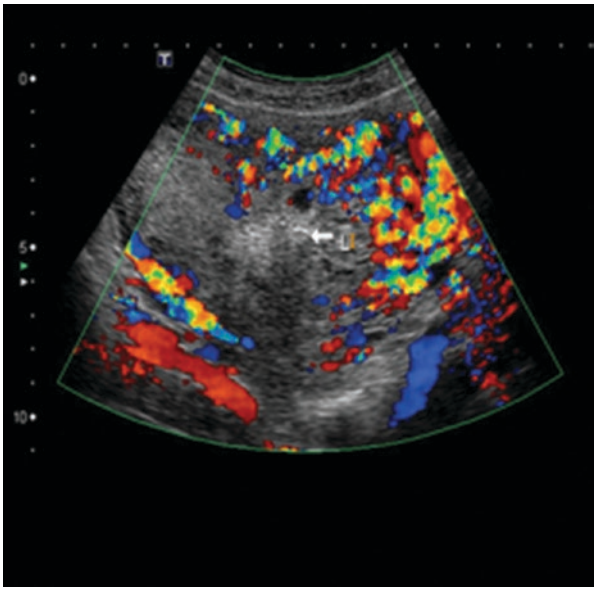

Fig. 6.7 Color Doppler study arteriovenous malformation in a patient with invasive mole recurrence, which is seen as a tangle of vessels in the uterus with color aliasing due to high flow

tangle of abnormal vessels at the nidus of the AVM with early venous filling. Super selective catheterization of the AVM with liquid embolization with glue or coil embolization may be performed to treat AVMs that present with bleed.

6.9 Conclusion and Key Points

Imaging plays a central role in the diagnosis, management, and the surveillance of gestational trophoblastic diseases.

- Ultrasound is the first imaging investigation of choice in the evaluation of bleeding during pregnancy.
- In patients with elevated β-hCG following evacuation of molar pregnancy, the main role of ultrasound is to exclude normal pregnancy.
- Measuring the size of the mass and the size of the uterus on ultrasound has prognostic significance.
- Doppler indices such as pulsatility index are useful in both diagnosing GTN and in predicting chemoresistance.
- In non-molar choriocarcinoma, staging evaluation should include CT of the thorax, abdomen, and pelvis (CT-TAP).
- In molar choriocarcinoma, CT abdomen pelvis and MR brain can be selectively done in patients with lung metastases.
- Symptomatic patients with AVMs following GTD can be treated with angio-embolization.

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