Access this article online

Quick Response Code:

Website: www.pogsjournal.org

DOI: 10.4103/pjog.pjog_18_23

The use of uterine artery Doppler studies as predictors for postmolar gestational trophoblastic neoplasia

Maria Febi Billones De Ramos[1], Lara Marie David Bustamante[1], Elizabeth Karunungan Jacinto[1]

Abstract:

BACKGROUND: Gestational trophoblastic neoplasia (GTN) is considered one of the most curable malignancies, especially when diagnosis and treatment are commenced early. Identifying predictors for the development of GTN will enable prompt management equating to an excellent prognosis.

OBJECTIVES: The objectives of this study were to determine the validity of uterine artery Doppler parameters (UADPs) as predictors for postmolar GTN, compare UADP values before and after evacuation, determine cutoff values and relationship with beta-human chorionic gonadotropin (hCG) levels.

MATERIALS AND METHODS: This was a prospective cohort study, which included histopathologically confirmed hydatidiform mole (HM) patients who underwent suction curettage. UADPs (pulsatility index (PI), resistive index, and systolic/diastolic [S/D] ratio) were measured preevacuation, 4 weeks postevacuation, and 6 weeks postevacuation. Patients were followed up to determine whether they will develop postmolar GTN or not.

RESULTS: A total of 31 HM patients were admitted during the study period, 84% (26/31) of whom underwent suction curettage. Of these, 92% (24/26) had histopathology of complete HM and were recruited. However, only 17 patients followed up and completed the study. Results showed that there was an increasing trend of the UADP from preevacuation to 6 weeks postevacuation and the trend between those with and without postmolar GTN was statistically significant. There was also an inverse relationship between the UADP and baseline β-hCG values. UADP showed lower values among patients who developed postmolar GTN compared to those who did not. The cutoff values recommended by the area under curve (AUC) that can be a possible predictor were 4th-week right PI of 2.14 (AUC = 0.71) and right S/D ratio of 2.60 (AUC = 0.73) and 6th-week left PI of 2.80 (AUC = 0.70) and right PI of 2.53 (AUC = 0.74).

CONCLUSION: Neoangiogenesis, a hallmark of malignancy, is correlated with invasive disease and will show increased myometrial vascularization with lower uterine artery indices. Doppler ultrasound may be a useful tool for postmolar follow-up and GTN diagnosis. However, the small sample size in this study is a limitation and a larger multicenter study is recommended.

Keywords:

Gestational trophoblastic neoplasia, hydatidiform mole, uterine artery diagnostic imaging

[1]Department of Obstetrics and Gynecology, University of the Philippines, Philippine General Hospital, Manila, Philippines

Address for correspondence:
Dr. Maria Febi Billones De Ramos, Department of Obstetrics and Gynecology, University of the Philippines, Philippine General Hospital, Manila, Philippines.
E-mail: mcbillonesderamos@up.edu.ph

Submitted: 05-Apr-2023
Revised: 08-May-2023
Accepted: 10-May-2023
Published: 27-Sep-2023

Introduction

Gestational trophoblastic disease refers to a broad spectrum of abnormal trophoblastic proliferation associated with pregnancy. Histologically, it includes the premalignant–complete or partial hydatidiform mole (HM) and the malignant-invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor, with the last four collectively known as gestational trophoblastic neoplasia (GTN).

How to cite this article: De Ramos MB, Bustamante LD, Jacinto EK. The use of uterine artery Doppler studies as predictors for postmolar gestational trophoblastic neoplasia. Philipp J Obstet Gynecol 2023;47:108-20.

GTN is considered one of the most curable diseases, especially when diagnosis and treatment are commenced early. Accurate diagnosis of HM is based on a combination of clinical history, physical examination, serum beta-human chorionic gonadotropin (hCG), and ultrasonographic findings. Over the years, the diagnosis of HM has improved, and the early detection is due to the increased availability of ultrasound and serum β-hCG measurement. The classic presenting signs and symptoms such as vaginal bleeding, excessive uterine enlargement, preeclampsia, hyperthyroidism, anemia, and hyperemesis are less frequently reported. However, vaginal bleeding is still the most common presenting symptom but has declined significantly by 46%.[1] The initial diagnostic imaging test is pelvic (two-dimensional) grayscale ultrasonography being noninvasive, cost-effective, and readily available with an overall sensitivity of 50%–68%,[2] and a specificity of 92.6%.[3] The risk for a complete mole to progress to GTN is 15%–25% compared to a much lower risk of about 0.5%–5% for a partial mole (PM).[2,4] Risk factors for postmolar GTN include advanced maternal age equal to 40 years old (≥40), serum β-hCG titers ≥100,000 mIU/mL, presence of theca lutein cysts ≥6 cm, a uterine size larger than the age of gestation of ≥6 weeks, presence of medical complication (preeclampsia or hyperthyroidism), recurrent HM, and documented coexisting twin mole with a live fetus. β-hCG, an effective tumor marker of the disease, is still the standard tool used for diagnosis and management including the detection of malignant degeneration. The initial postevacuation β-hCG titer will initially show a lower level from baseline since the entire molar pregnancy is evacuated. However, serial titers are needed to detect persistent disease. A rise or plateau of β-hCG titers during serial monitoring postevacuation will determine whether malignant degeneration developed. However, high-risk patients who will develop postmolar GTN will not be predicted by the initial or postevacuation β-hCG levels.

Table 1: Demographic data of patients included (*n*=17)

Demographic data	Descriptive, *n* (%)
Age (years), mean±SD	25.53±5.85
Gravidity	
Gravidity <4	15 (88.2)
Gravidity ≥4	2 (11.8)
Parity	
P0	7 (41.2)
P1	6 (35.3)
P2	2 (11.8)
P3	1 (5.9)
P4	1 (5.9)
Presence of theca lutein cysts	
None	10 (58.8)
Yes	7 (41.2)
Chemoprophylaxis given	
No	3 (17.6)
Yes	14 (82.4)
Baseline β-hCG (mIU/mL), mean±SD	762,152.67±526,384.39
Volume of molar gestation on ultrasound (cc)	418

SD: Standard deviation, β-hCG: Beta-human chorionic gonadotropin

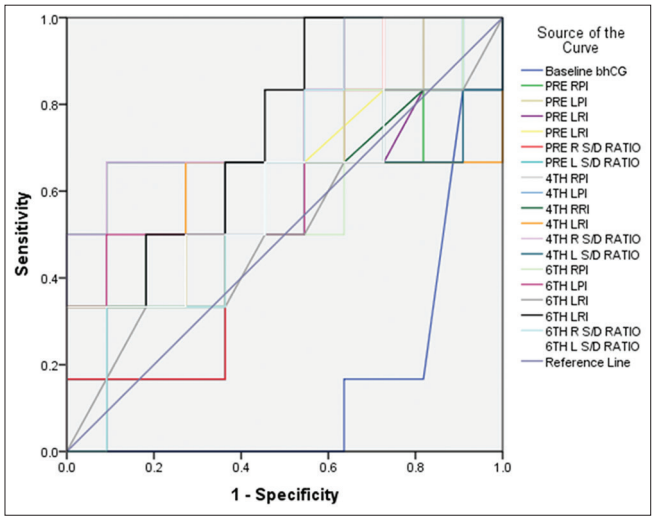

Figure 1: Area under curve index of baseline β-hCG, PI, RI, and S/D ratio in predicting postmolar gestational trophoblastic neoplasia. β-hCG: Beta-human chorionic gonadotropin, PI: Pulsatility index, RI: Resistive index, S/D ratio: Systolic/diastolic ratio

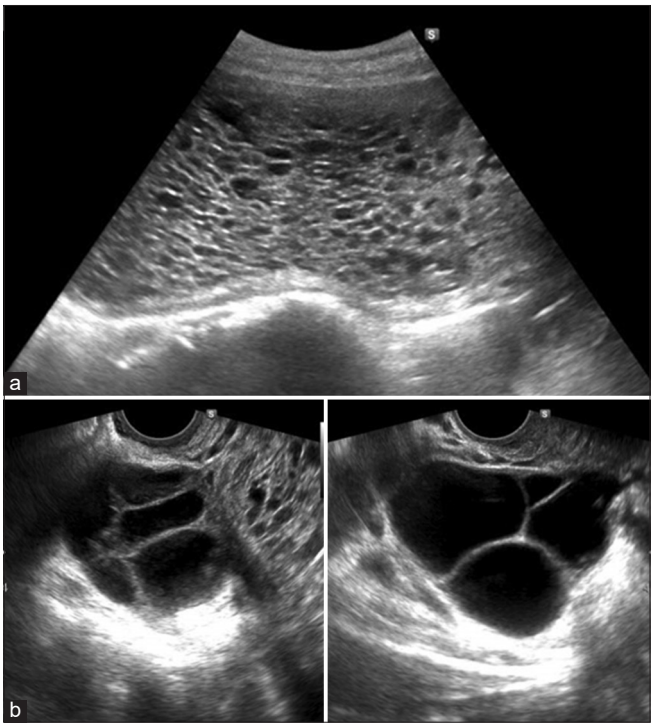

Figure 2: Picture of hydatidiform mole with bilateral theca lutein cysts. 26 years old, G2P1, 16 3/7 weeks AOG, serum beta-human chorionic gonadotropin 112,500 mIU/mL showing endometrial contents with "snowstorm" pattern (a) and bilateral theca lutein cysts (b)

Angiogenesis is among the hallmarks of malignancy and GTN being a highly vascular tumor can be further

Table 2: Outcome of patients (*n*=17)

Outcomes	Descriptive
Postmolar gestational trophoblastic neoplasia, *n* (%)	
No	11 (64.7)
Yes	6 (35.3)
Time until normal β-hCG (days), mean±SD	89.27±23.51
Time to develop to postmolar GTN (days), mean±SD	57.67±16.97

SD: Standard deviation, GTN: Gestational trophoblastic neoplasia, β-hCG: Beta-human chorionic gonadotropin

Table 3: Patients' pulsatility index, resistive index, and systolic/diastolic ratio from preevacuation to 6th week

Uterine artery Doppler parameters	Preevacuation	4th week	6th week	*P*
PI				
Right	1.90±0.86	2.31±0.75	2.44±0.71	0.021
Left	2.03±0.90	2.14±0.65	2.62±0.83	0.036
RI				
Right	0.76±0.12	0.82±0.10	0.85±0.08	0.002
Left	0.79±0.13	0.82±0.11	0.87±0.08	0.020
S/D ratio				
Right	6.03±3.76	7.60±4.72	8.64±5.44	0.027
Left	5.15±2.63	6.96±4.45	14.48±22.4	0.086

PI: Pulsatility index, RI: Resistive index, S/D ratio: Systolic/diastolic ratio

evaluated using Doppler ultrasound in addition to grayscale imaging. It has become an important diagnostic tool to evaluate and describe tumoral blood flow confirming the diagnosis of postmolar GTN in addition to rising or plateauing β-hCG titers. The presence of an invasive vascular mass following molar evacuation is a diagnostic finding. Few studies have evaluated the role of Doppler ultrasound, specifically the use of uterine artery Doppler indices with their correlation on β-hCG levels and as predictors for *methotrexate* chemoresistance.[5-8] Data in the literature remain controversial, though most studies have noted that a lower resistance in the uterine artery may be associated with GTN.[9-11] However, its role as a predictor prior to the appearance of a visible tumor has not yet been established.

Despite the earlier diagnosis of HM, the risk of development to postmolar GTN did not change. Identifying predictors for the early detection of GTN is very important because it will enable prompt diagnosis equating to early chemotherapy and excellent prognosis. The significance of the study is to be able to determine the validity of uterine artery Doppler parameters (UADPs) as a possible predictor of postmolar GTN, to know a cutoff value that will determine progression to GTN, and to establish a relationship with β-hCG levels and UADP.

Research objectives

General objective

The general objective of this study was to determine the validity of UADPs as predictors for postmolar GTN.

Specific objectives

The specific objectives of this study were as follows:

1. To compare UADP before and after HM evacuation between women with postmolar GTN and women with spontaneous normalization of serum β-hCG
2. To determine the best parameters and cutoff values for GTN prediction
3. To know the relationship of UADP to β-hCG levels of HM patients.

Materials and Methods

This was a prospective cohort study which included all histopathologically confirmed patients diagnosed with HM who subsequently underwent suction curettage in a tertiary government hospital from April to August 2017. Only patients who consented to be included in the study were included. Patients who underwent hysterectomy with mole *in situ* and those with histopathology of nonmolar gestation, partial HM, and choriocarcinoma were excluded from the study.

Description of the study procedure

The study protocol underwent technical review by the department research technical review board and was approved by the hospital research ethics board. Participant information and data gathered in the study were kept confidential. Subjects were approached for enrollment if they had a diagnosis of HM supported by clinical history and physical examination, elevated serum β-hCG, and sonologic evidence of a molar pregnancy. The procedure of the study was explained to the eligible subjects by the primary investigator and informed consent was obtained. Demographic information and clinical data were recorded in the patient datasheet [Appendix A].

Baseline transvaginal ultrasound (TVS) with UADP was measured and recorded prior to evacuation of the molar pregnancy. Ultrasound triplex system (B-mode with color flow and pulsed wave Doppler) using a 5–10 MHz frequency transvaginal probe (Samsung Accuvix A30) was used to measure the UADP, which included pulsatility index (PI), resistive index (RI), and systolic/diastolic ratio (S/D ratio). The transvaginal probe was inserted into the vagina and placed in the lateral fornix, and the ascending branch of the uterine artery was identified on both sides. Pulsed wave Doppler was applied with the sampling gate set at 2 mm with an angle of insonation of 30°–45°. Three measurements of the UADP on both sides were obtained using auto trace and the average value was recorded.

The standard management for HM patients was rendered by the fellows of the division of trophoblastic diseases.

Table 4: Test of linear relationship among pulsatility index, resistive index, systolic/diastolic ratio, and baseline β-hCG values

Variables correlated with Baseline β-hCG	Pearson *r*	*P*
Pre-evacuation		
Pulsatility index		
right	-0.096	0.714
left	0.084	0.748
Resistive Index		
right	-0.148	0.570
left	0.147	0.573
S/D Ratio		
right	-0.047	0.858
left	-0.283	0.271
4th week		
Pulsatility index		
right	-0.343	0.178
left	-0.112	0.670
Resistive Index		
right	-0.139	0.596
left	0.014	0.956
S/D Ratio		
right	0.087	0.739
left	0.022	0.933
6th week		
Pulsatility index		
right	-0.403	0.109
left	-0.577	0.015
Resistive Index		
right	-0.269	0.297
left	-0.521	0.032
S/D Ratio		
right	-0.282	0.273
left	-0.427	0.088

Patients were managed accordingly and were advised for serial serum β-hCG monitoring postevacuation. Final histopathology results were also retrieved and recorded during follow-up. A histopathology result of nonmolar gestation, partial HM, or choriocarcinoma was excluded from the study.

Repeat TVS with UADP was performed on the eligible patients 4 and 6 weeks postmolar evacuation. The values of the PI, RI, and S/D ratio were recorded. β-hCG levels were serially determined until normal values were obtained or up to the time that a diagnosis of postmolar GTN was established. The main outcome of this study was to determine if UADP can be used as a predictor for postmolar GTN.

Results

There were a total of 31 HM admissions diagnosed by clinical history and physical examination, elevated β-hCG, and an ultrasound finding of a molar pregnancy admitted during the study period. There were 26 (84%) patients who underwent suction curettage as a form of molar evacuation while 5 (16%) patients underwent total hysterectomy with mole *in situ*. Patients who underwent suction curettage were the only patients included in the study.

Among the 26 patients who underwent suction curettage, 24 (92%) had a final histopathology result of a complete HM while 2 (8%) had a partial HM versus hydropic placenta, hence the latter were excluded. However, there were 5 patients who were lost to follow-up and 2 patients who did not complete the study. Hence, a total of 17 patients were subsequently followed up to determine whether they will develop postmolar GTN or not.

Table 1 shows the demographic profile of patients showing a mean age in years of 25.53 ± 5.85. Fifteen (88.2%) of the patients were with gravidity of <4, with 7 (41.2%) of the patients being primigravid. The mean baseline β-hCG is 762,152.67 ± 526,384.39 mIU/mL. Ten patients (58.8%) were reported to have theca lutein cysts [Figure 2] while seven patients (41.2%) did not have. Fourteen patients (82.4%) were given chemoprophylaxis while three patients (17.6%) did not. The mean volume of molar products on ultrasound of all the patients was 418 cc. Table 2 shows the outcome of the 17 patients, 11 (64.7%) of which eventually had normal β-hCG while 6 (35.3%) had either plateauing or rising β-hCG titers during follow-up and were diagnosed with postmolar GTN. The average duration among patients who eventually had normal β-hCG is 89.27 ± 23.51 days compared to 57.67 ± 16.97 days among patients who developed postmolar GTN.

Table 3 shows the UADP values of all the patients included in the study from preevacuation to the 6th week postevacuation. All the values were noted to be increasing in trend from preevacuation until 6 weeks postevacuation. Table 4 shows a test of linear relationship among PI, RI, S/D ratio, and baseline β-hCG values which showed that there was an inverse relationship between the left PI and baseline β-hCG (r = –0.577, P = 0.015) and left RI and baseline β-hCG (r = –0.521, P = 0.032). An inverse relationship implied that when the PI and RI values were high, the baseline β-hCG values were low and vice versa. The mean baseline β-hCG among patients who developed postmolar GTN was 1,108,869.69 ± 443,038.95 mIU/mL and was higher compared to 573,034.29 ± 483,442.99 mIU/mL among patients who did not, as shown in Table 5. PI, RI, and S/D ratio of patients who did not develop postmolar GTN showed an increasing trend from preevacuation until the 6th week postevacuation [Figures 3 and 4]. However, an increasing trend was also noted among

Table 5: Comparisons of baseline beta-human chorionic gonadotropin, pulsatility index, resistive index, and systolic/diastolic ratio between those with and without postmolar gestational trophoblastic neoplasia

Parameters	Mean±SD			*P*
	Postmolar gestational trophoblastic neoplasia		Total	
	No	Yes		
Baseline β-hCG (mIU/mL)	573,034.29±483,442.99	1,108,869.69±443,038.95	762,152.67±526,384.39	0.040
Preevacuation				
PI				
Right	1.99±0.94	1.73±0.77	1.90±0.86	0.570
Left	2.22±0.90	1.67±0.86	2.03±0.90	0.237
RI				
Right	0.77±0.12	0.74±0.12	0.76±0.12	0.711
Left	0.82±0.10	0.73±0.15	0.79±0.13	0.178
S/D ratio				
Right	6.66±4.21	4.87±2.71	6.03±3.76	0.368
Left	5.32±2.69	4.86±2.73	5.15±2.63	0.742
4th week				
PI				
Right	2.54±0.59	1.89±0.88	2.31±0.75	0.084
Left	2.26±0.48	1.93±0.90	2.14±0.65	0.325
RI				
Right	0.85±0.05	0.77±0.14	0.82±0.10	0.094
Left	0.84±0.06	0.78±0.18	0.82±0.11	0.334
S/D ratio				
Right	7.70±2.46	7.42±7.68	7.60±4.72	0.912
Left	6.46±2.99	7.88±6.63	6.96±4.45	0.547
6th week				
PI				
Right	2.53±0.71	2.29±0.74	2.44±0.71	0.522
Left	2.82±0.86	2.25±0.69	2.62±0.83	0.181
RI				
Right	0.85±0.08	0.85±0.09	0.85±0.08	0.936
Left	0.89±0.07	0.83±0.07	0.87±0.08	0.126
S/D ratio				
Right	9.89±6.33	6.33±2.16	8.64±5.44	0.207
Left	18.48±27.36	7.16±2.97	14.48±22.40	0.335

PI: Pulsatility index, RI: Resistive index, S/D ratio: Systolic/diastolic ratio, β-hCG: Beta-human chorionic gonadotropin

patients who developed postmolar GTN but with lower values [Figures 5 and 6].

Figure 1 show an illustration of the area under the curve (AUC) of the baseline β-hCG, PI, RI, and S/D Ratio values in predicting post-molar GTN. As noted in Table 6, the parameters which demonstrated clinically acceptable performance were as follows: 4th-week right PI (AUC = 0.71), 4th-week right S/D ratio (AUC = 0.73), 6th-week left PI (AUC = 0.70), and 6th-week right PI (AUC = 0.74). Table 7 shows the cutoff values recommended by AUC showing its sensitivity and specificity, likelihood ratio, and positive and negative predictive values.

Discussion

The Philippine Society for the Study of Trophoblastic Diseases recommends monitoring of serum β-hCG 1 week after molar evacuation then repeat every 2 weeks until the level becomes normal (<5 mIU/ml). After 2 consecutive biweekly normal levels, β-hCG monitoring is done every month for 6 months.[2] Diligent monitoring is advised after molar evacuation to detect malignant degeneration. However, there is no established tumor marker to predict who among the HM patients will develop GTN. The clearance rate of β-hCG is constant and the interval time for achieving a normal value depends on the baseline levels. The higher the baseline, the longer the time to achieve normal values. Furthermore, more than half of the patients will have undetectable β-hCG within 8 weeks postevacuation.[2,12] The diagnosis of postmolar GTN is considered if any of the following criteria is met:[2,4,12] (a) plateauing β-hCG levels for four consecutive weekly measurements for at least 3 weeks (days 0, 7, 14, and 21); (b) rising β-hCG levels for three consecutive weekly measurements or longer for at least 2 weeks (days 0, 7, and 14); and (c) a histologic diagnosis of choriocarcinoma.

The results of the study showed that 35.3% had postmolar GTN with an average duration of 57.67 ± 16.97 days. The interval duration in developing postmolar GTN was noted to be shorter compared to β-hCG normalization. Patients who presented with either bleeding or rising or plateauing β-hCG titers were already diagnosed with postmolar GTN while those patients who had decreasing β-hCG titers continued monitoring up to the time that normal values were obtained. Therefore, the patients who did not progress to GTN had a longer duration of β-hCG monitoring.

Table 6: Area under curve index of baseline beta- human chorionic gonadotropin, pulsatility index, resistive index, and systolic/diastolic ratio in predicting postmolar gestational trophoblastic neoplasia

Test result variable(s)	AUC	SE	Remarks
Baseline β-hCG	0.15	0.10	Below AUC 0.70
			As clinically acceptable accuracy
Preevacuation			
Right PI	0.55	0.15	Below AUC 0.70
			As clinically acceptable accuracy
Left PI	0.67	0.15	Below AUC 0.70
			As clinically acceptable accuracy
Right RI	0.55	0.15	Below AUC 0.70
			As clinically acceptable accuracy
Left RI	0.67	0.15	Below AUC 0.70
			As clinically acceptable accuracy
Right S/D ratio	0.59	0.14	Below AUC 0.70
			As clinically acceptable accuracy
Left S/D ratio	0.56	0.15	Below AUC 0.70
			As clinically acceptable accuracy
4th week postevacuation			
Right PI	0.71	0.15	Within clinically acceptable limit
Left PI	0.61	0.17	Below AUC 0.70
			As clinically acceptable accuracy
Right RI	0.70	0.17	Below AUC 0.70
			As clinically acceptable accuracy
Left RI	0.58	0.18	Below AUC 0.70
			As clinically acceptable accuracy
Right S/D ratio	0.73	0.16	Within clinically acceptable limit
Left S/D ratio	0.53	0.17	Below AUC 0.70
			As clinically acceptable accuracy
6th week postevacuation			
Right PI	0.58	0.16	Below AUC 0.70
			As clinically acceptable accuracy
Left PI	0.70	0.14	Within clinically acceptable limit
Right RI	0.52	0.16	Below AUC 0.70
			As clinically acceptable accuracy
Left RI	0.74	0.12	Within clinically acceptable limit
Right S/D ratio	0.64	0.14	Below AUC 0.70
			As clinically acceptable accuracy
Left S/D ratio	0.64	0.15	Below AUC 0.70
			As clinically acceptable accuracy

PI: Pulsatility index, RI: Resistive index, AUC: Area under curve, S/D ratio: Systolic/diastolic ratio, β-hCG: Beta-human chorionic gonadotropin, SE: Standard error

Molar pregnancy in the first and early trimesters will show high velocity and low impedance waveforms due to a high degree of arterial invasion caused by abnormal proliferation of the trophoblasts.[10,11] The vascular impedance can be quantified using indices derived from the uterine artery waveform known as PI and resistive index (RI).[8] In GTN, TVS with color flow Doppler not only confirms the diagnosis but also determines the degree of myometrial invasion and the extent of disease in the adnexa or parametria. It likewise detects recurrence and evaluates good response during chemotherapy.[13-15] Although there is no consensus on the cutoff values, it has been observed in some studies that a PI of <1.5 and an RI of <0.4 are suggestive of GTN.[10,11,15,16]

Some studies support the importance and role of Doppler ultrasound using uterine artery indices in the management of patients with GTN and a lower resistance in the uterine artery was associated with the persistent disease although a larger sample size was recommended.[6-8,14,17,18] As reflected in Table 3, comparing the uterine blood flow before and after molar evacuation, there was an increasing trend of all the UADPs from preevacuation until 6 weeks postevacuation, and were all noted to be statistically significant. It is consistent with the study done by Amin *et al*.[7] wherein there was a continuous increase of all Doppler indices from preevacuation level to the 6th week postevacuation. As also shown in Table 4, the variables which were significantly correlated with baseline β-hCG values implied an inverse relationship that when the PI and RI values were high, the baseline β-hCG values were low and vice versa. The rest of the values based on the other phases were not statistically significant.

However, when comparisons of baseline β-hCG, PI, RI, and S/D ratio between those with and without postmolar GTN were done [Table 5], only the baseline β-hCG values were significantly different (with PM-GTN 1,108,869.69 vs. without PM-GTN 573,034.29, $P = 0.040$). UADP showed lower values among patients who develop postmolar GTN compared to those who did not have postmolar GTN, but the difference between them was not statistically significant.

AUC is a standardized measurement to assess the risk scoring tool in its accuracy performance in predicting an outcome. The values of UADP and baseline β-hCG of all patients were used to look for a pattern whether a higher or lower value was predictive of postmolar GTN. Based on standardized interpretation, if an AUC generated by a scoring system reaches an index of 0.70 and above, the risk scoring tool will demonstrate a clinically acceptable accuracy in predicting an outcome. Those with AUC below 0.70 are considered not clinically acceptable. In this study, the cutoff values

recommended by AUC that can be a possible predictor are 4th-week right PI of 2.14 (AUC = 0.71) and right S/D ratio of 2.60 (AUC = 0.73) and 6th-week left PI of 2.80 (AUC = 0.70) and right PI of 2.53 (AUC = 0.74). However, the sensitivity and specificity were relatively low. Figures 2-5 show some of the representations of the uterine artery indices in a patient who eventually had normal β-hCG and in a patient who developed postmolar GTN. In a recent similar published study by Asmar *et al*.,[15] uterine artery Doppler flow velocimetry, particularly the PI, showed that a preevacuation cutoff value of 1.38 (77% sensitivity and 82% specificity) and a postevacuation cutoff value of 1.77 (79% sensitivity and 86% specificity) were significantly useful in predicting postmolar GTN.

Conclusion

Neoangiogenesis, as a hallmark of malignancy, is seen in postmolar GTN wherein increased myometrial

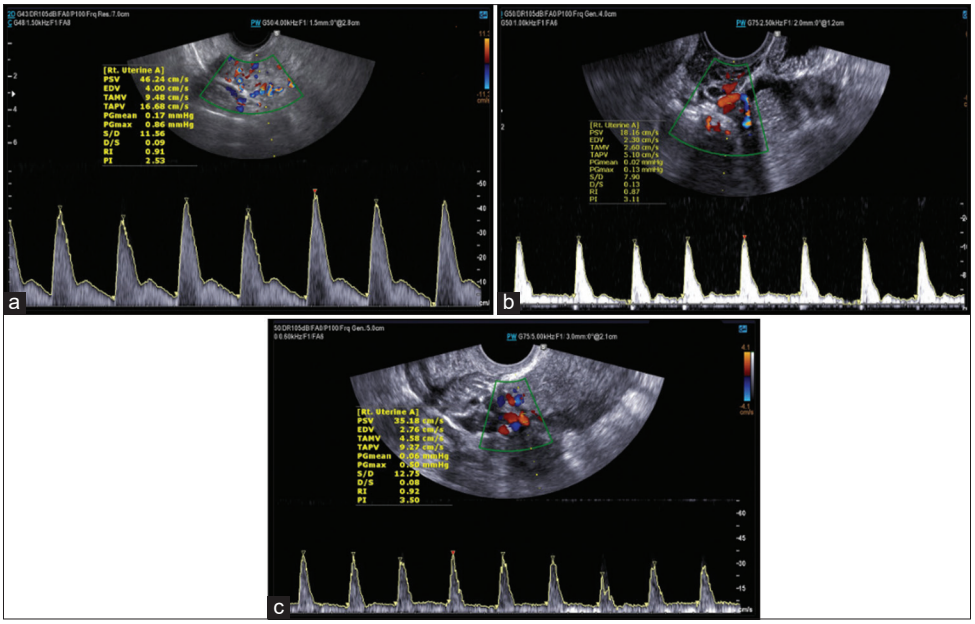

Figure 3: Right uterine artery indices in a patient who eventually had normal β-hCG. There is an increasing trend of the right pulsatility index. (a) Preevacuation. (b) Fourth week postevacuation. (c) Sixth week postevacuation. β-hCG: Beta-human chorionic gonadotropin

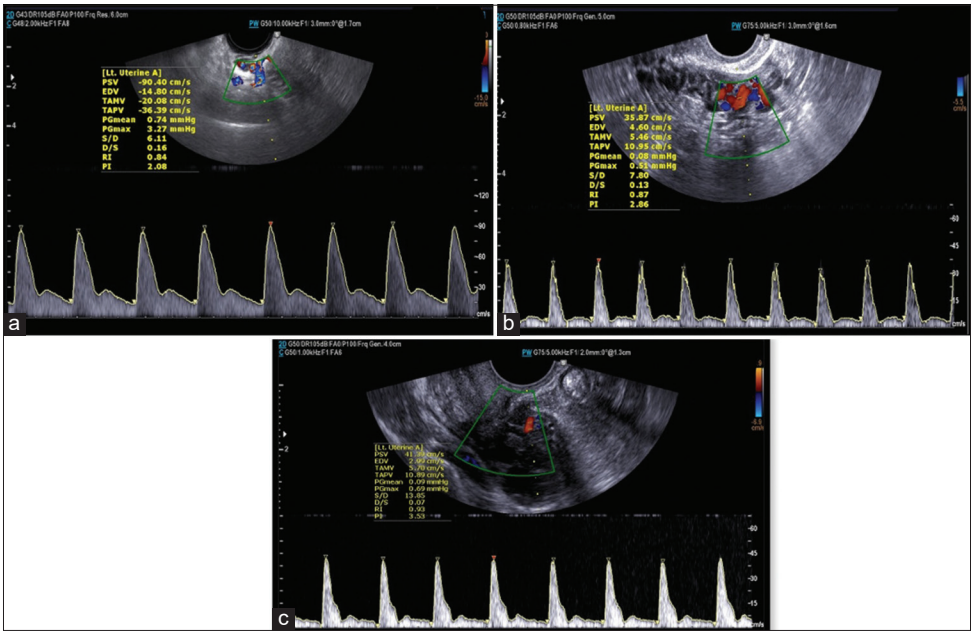

Figure 4: Left uterine artery indices in a patient who eventually had normal β-hCG. There is also an increasing trend of the left pulsatility index. (a) Preevacuation. (b) Fourth week postevacuation. (c) Sixth week postevacuation. β-hCG: Beta-human chorionic gonadotropin

Table 7: Recommended cutoff values recommended from the area under curve

Parameter	Cutoff recommended by AUC	Sensitivity (%)	Specificity (%)	Likelihood ratio +	Positive predictive value (%)	Negative predictive value (%)
Preevacuation						
PI						
Right	2.26	33.3	63.6	0.92	33	64
Left	2.51	16.7	63.6	0.46	20	58
RI						
Right	0.76	33.3	36.4	0.52	22	50
Left	0.77	50.0	27.3	0.69	27	50
S/D ratio						
Right	8.59	16.7	72.7	0.61	25	62
Left	5.54	33.3	54.6	0.73	29	60
4th week						
PI						
Right	2.14	33.3	27.3	0.46	20	43
Left	1.96	50.0	18.2	0.61	25	40
RI						
Right	0.80	33.3	18.2	0.41	18	33
Left	0.74	66.7	9.1	0.73	29	33
S/D ratio						
Right	2.60	83.3	0.0	0.83	31	0
Left	10.56	33.3	90.9	3.67	67	71
6th week						
PI						
Right	2.53	33.3	63.6	0.92	33	64
Left	2.80	16.7	63.6	0.46	20	58
RI						
Right	0.86	33.3	63.6	0.92	33	64
Left	0.86	50.0	36.4	0.79	30	57
S/D ratio						
Right	3.71	100.0	9.1	1.10	38	100
Left	3.93	83.3	0.0	0.83	31	0

PI: Pulsatility index, RI: Resistive index, AUC: Area under curve, S/D ratio: Systolic/diastolic ratio

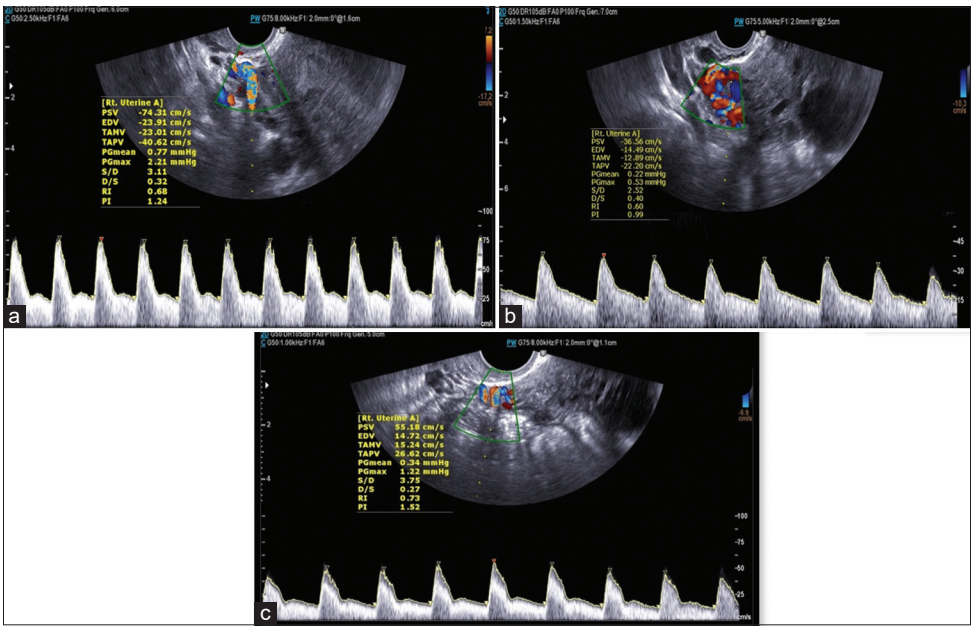

Figure 5: Right uterine artery indices in a patient who developed postmolar gestational trophoblastic neoplasia. (a) Preevacuation (b) Fourth week postevacuation. (c) Sixth week postevacuation.

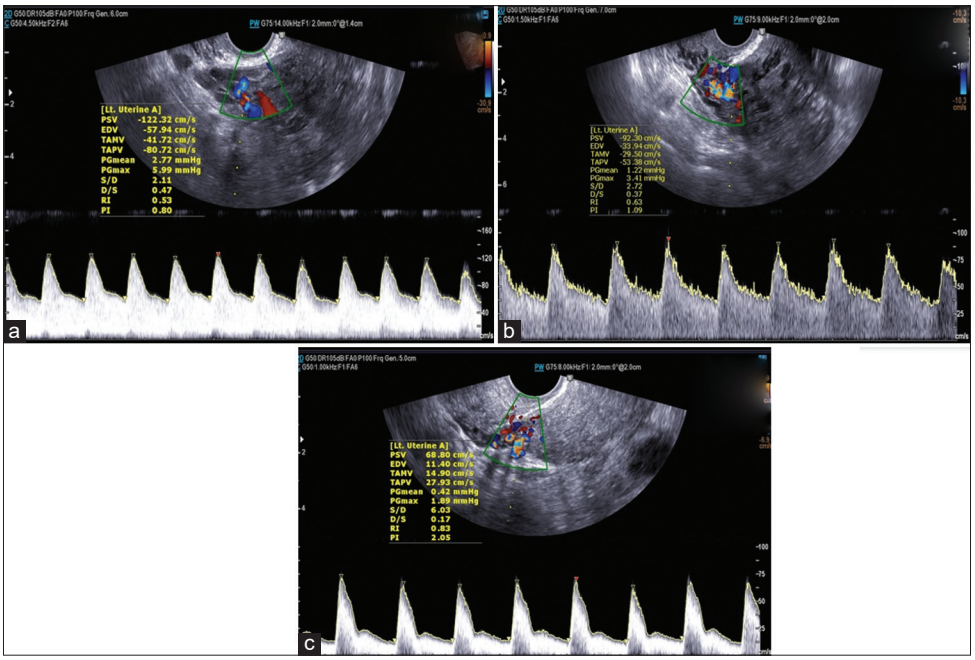

Figure 6: Left uterine artery indices in a patient who developed postmolar gestational trophoblastic neoplasia. (a) Preevacuation. (b) Fourth week postevacuation (c) Sixth week postevacuation

vascularization with lower uterine artery indices is noted on Doppler ultrasound. Based on the study, Doppler ultrasound may seem useful as a predictor for postmolar GTN. The UADP showed an increasing trend postevacuation which was inversely proportional to the decreasing trend of β-hCG among patients who had spontaneous normalization of β-hCG. However, a similar trend was also observed among patients who developed postmolar GTN but with lower values. Cutoff values were determined though the sensitivity and specificity were relatively low.

Limitations and recommendations

There are several applications of Doppler ultrasound, and this study can be a pilot study for determining the validity of UADP as a predictor for postmolar GTN. However, a larger multicenter study is recommended to better evaluate these findings and to help clinicians in the management and counseling of trophoblastic patients. It is also suggested to do a follow-up of patients until the normalization of β-hCG for 6 months.

Authorship contributions

Maria Febi Billones De Ramos - Involved in the conceptualization, methodology, resources, data curation, writing of original draft, review and editing.

Lara Marie David Bustamante - Involved in the conceptualization, methodology, validation of the technique, review and editing of the draft, and supervision.

Elizabeth Karunungan Jacinto - Involved in the conceptualization, methodology, review and editing of the draft, and supervision.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Sun SY, Melamed A, Goldstein DP, Bernstein MR, Horowitz NS, Moron AF, *et al.* Changing presentation of complete hydatidiform mole at the New England trophoblastic disease center over the past three decades: Does early diagnosis alter risk for gestational trophoblastic neoplasia? Gynecol Oncol 2015;138:46-9.
2. Estrella A, Llarena, R. In: Hydatidiform Mole. Clinical Practice Guidelines for the diagnosis and management of Gestational Trophoblastic Diseases. Philippine Society for the Study of Trophoblastic Diseases, Inc: Diliman, Quezon City; 2016. p. 10-22.
3. Newhouse I, Spacey A, Scragg B, Szczepura K. The diagnostic value and accuracy of ultrasound in diagnosing hydatidiform mole: A systematic review and meta-analysis of the literature. Radiography (Lond) 2022;28:897-905.
4. Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, *et al.* Diagnosis and management of gestational trophoblastic disease: 2021 update. Int J Gynaecol Obstet 2021;155 Suppl 1:86-93.
5. Chan FY, Chau MT, Pun TC, Lam C, Ngan HY, Wong RL. A comparison of colour Doppler sonography and the pelvic arteriogram in assessment of patients with gestational trophoblastic disease. Br J Obstet Gynaecol 1995;102:720-5.
6. Lin LH, Bernardes LS, Hase EA, Fushida K, Francisco RP. Is Doppler ultrasound useful for evaluating gestational trophoblastic disease? Clinics (Sao Paulo) 2015;70:810-5.
7. Amin NS, Yassen RN, Abd-EL-Kareem HF, Al-Sabbagh AA.

Uterine Artery Doppler Blood flow in Cases of Hydatidiform Mole and its Correlation with β-hCG. Iraqi J Community Med 2014;27(1:1-9).

8. Agarwal R, Harding V, Short D, Fisher RA, Sebire NJ, Harvey R, *et al*. Uterine artery pulsatility index: A predictor of methotrexate resistance in gestational trophoblastic neoplasia. Br J Cancer 2012;106:1089-94.
9. Malek M, Moradi B, Mousavi AS, Ahmadinejad N, Kazemi MA, Gity M. Complementary role of ultrasound in management of gestational trophoblastic disease. Iran J Radiol 2015;12:e13955.
10. Dhanda S, Ramani S, Thakur M. Gestational trophoblastic disease: A multimodality imaging approach with impact on diagnosis and management. Radiol Res Pract 2014;2014:842751.
11. Lima LL, Parente RC, Maestá I, Amim Junior J, de Rezende Filho JF, Montenegro CA, *et al*. Clinical and radiological correlations in patients with gestational trophoblastic disease. Radiol Bras 2016;49:241-50.
12. Lurain JR. Gestational trophoblastic disease I: Epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol 2010;203:531-9.
13. Kani KK, Lee JH, Dighe M, Moshiri M, Kolokythas O, Dubinsky T. Gestatational trophoblastic disease: Multimodality imaging assessment with special emphasis on spectrum of abnormalities and value of imaging in staging and management of disease. Curr Probl Diagn Radiol 2012;41:1-10.
14. Long MG, Boultbee JE, Langley R, Newlands ES, Begent RH, Bagshawe KD. Doppler assessment of the uterine circulation and the clinical behaviour of gestational trophoblastic tumours requiring chemotherapy. Br J Cancer 1992;66:883-7.
15. Asmar FT, Braga-Neto AR, de Rezende-Filho J, Villas-Boas JM, Charry RC, Maesta I. Uterine artery Doppler flow velocimetry parameters for predicting gestational trophoblastic neoplasia after complete hydatidiform mole, a prospective cohort study. Clinics (Sao Paulo) 2017;72:284-8.
16. Zhou Q, Lei XY, Xie Q, Cardoza JD. Sonographic and Doppler imaging in the diagnosis and treatment of gestational trophoblastic disease: A 12-year experience. J Ultrasound Med 2005;24:15-24.
17. Tsuyoshi H, Sugita G, Kurokawa T, Yoshida Y. Color Doppler sonography as an adjunct to repeat uterine evacuation for gestational trophoblastic disease: Case report. J Clin Ultrasound 2013;41 Suppl 1:54-8.
18. Garavaglia E, Gentile C, Cavoretto P, Spagnolo D, Valsecchi L, Mangili G. Ultrasound imaging after evacuation as an adjunct to beta-hCG monitoring in posthydatidiform molar gestational trophoblastic neoplasia. Am J Obstet Gynecol 2009;200:417.e1-5.

APPENDIX A

Computation of sample size

As reported in the study of Amin *et al.* (2014),[7] the incidence of HM is well known to be highest in Southeast Asia with rates ranging 1–2/1000 pregnancies, assuming that the rate of HM is at 0.20%, estimated at a precision of ±2% estimated at CI 95%, then the computed representative sample in this study is 20.

Proportion	Infinite *n*
n (population size)	Infinite
p (expected proportion)	0.002
d (precision)	0.200
z alpha/2 (95% CI)	1.96
n - num	0.0077
n - den	0.0002
Sample size (*n*)	20

CI: Confidence interval

The sample size of 20 is feasible in the local setting considering that there are usually 2–3 admissions of HM per week. These patients will be followed up until the first normal serum β-hCG.

Sample size equation

Sample size-infinite population

$$SS = \frac{Z^2 \times (p) \times (1-p)}{C^2}$$

SS: Sample size

Z: *Z*-value[A] (e.g., 1.96 for a 95% confidence interval)

p: Percentage of population picking a choice, expressed as decimal[B]

C: Confidence interval, expressed as decimal (e.g., 0.40 = ±4 percentage points)

A *Z*-value (cumulative normal probability table) represents the probability that a sample will fall within a certain distribution.

The *Z*-value for confidence levels are:
1.645 = 90% confidence level
1.96 = 95% confidence level
2.576 = 99% confidence level.

Sample size (20) = ([1.96]² × [0.002] × [1-0.002])/(0.020)²

Moreover, the power of sample size of 20 is at 83.5% to detect a moderate relationship between any of uterine artery Doppler parameters such as pulsatility index (PI), resistive index (RI), and systolic/diastolic ratio (S/D) on β-hCG in reference to the study of Amin *et al.*,[7] that there is a strong correlation between the fall in serum level of β-hCG and the rise of Doppler indices throughout the course of follow-up.

One correlation power analysis

Numeric results when Ha: R0<>R1

Power	*n*	Alpha	Beta	R0	R1
0.83553	20	0.05000	0.16447	0.00000	0.60000

Report definitions

- Power is the probability of rejecting a false null hypothesis. It should be close to one
- N is the size of the sample drawn from the population. To conserve resources, it should be small
- Alpha is the probability of rejecting a true null hypothesis. It should be small
- Beta is the probability of accepting a false null hypothesis. It should be small
- R0 is the value of the population correlation under the null hypothesis
- R1 is the value of the population correlation under the alternative hypothesis.

Summary statements

- A sample size of 20 achieves 83.5% power to detect a difference of −0.60,000 between the null hypothesis correlation of 0.00,000 and the alternative hypothesis correlation of 0.60,000 using a two-sided hypothesis test with a significance level of 0.05.

Statistical analysis

All the data were encoded and tabulated using the data processing software, Microsoft Excel, and were collated, and checked periodically for consistency and completeness. Uterine artery Doppler parameters such as pulsatility index (PI), resistive index (RI), and systolic/diastolic ratio (S/D) and β-hCG levels of patients were described using mean and standard deviation while profiling of patients' final histopathology results was expressed in frequency and percentages. In testing the correlations among pulsatility index (PI), resistive index (RI), and systolic/diastolic ratio (S/D) and β-hCG levels, an initial bivariate correlation was done; afterward, multiple linear regression was employed to test whether these parameters could predict the level of β-hCG. Moreover, the area under curve was computed for each of uterine artery Doppler parameter in predicting postmolar GTN to identify which cutoff values of each parameter would yield higher accuracy such as sensitivity, specificity, likelihood ratio, and negative and positive predictive values. Furthermore, 2 × 2 Fisher's exact test was employed to establish an association among uterine artery Doppler parameters cutoff values and postmolar gestational trophoblastic neoplasia. Any associated $P < 0.05$ alpha will be considered significant. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

PATIENT DATASHEET

IRB Approval Code: (OBG) 2017-185-01

Demographics:

Age/OB score:
Contact number:

Clinical data:

Baseline β-hCG (mIU/mL):
Presence of theca lutein cysts:
Chemoprophylaxis given: Yes No
Volume of molar gestation on ultrasound:

Post molar gestational trophoblastic neoplasia: Yes No
If Yes, Time (days) to develop to post molar GTN: _____
If No, Time (days) until with normal β-hCG post evacuation: _____

Ultrasound/Doppler results

Uterine artery	PI	RI	S/D ratio	β-hCG levels
Preevacuation				
Right				
Left				
4 weeks postevacuation				
Right				
Left				
6 weeks postevacuation				
Right				
Left				

PI: Pulsatility index, RI: Resistive index, S/D ratio: Systolic/diastolic ratio, β-hCG: Beta-human chorionic gonadotropin