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Correlation of uterine artery Doppler flow velocimetry and β-human chorionic gonadotropin levels during postmolar evacuation surveillance: A pilot study in a tertiary hospital

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Abstract:

BACKGROUND: During postmolar evacuation surveillance, beta-human chorionic gonadotropin (β-hCG) regression levels can predict invasive disease while Doppler ultrasound can assess *in vivo* tumor neovascularization and quantify uterine blood supply. As an ancillary tool to β-hCG monitoring, ultrasound can detect the early presence of viable trophoblastic tissues and identify patients at risk of developing postmolar gestational trophoblastic Neoplasia (PMGTN).

OBJECTIVE: The objective of this study was to correlate uterine artery Doppler ultrasound with β-hCG levels during pre- and postmolar evacuation surveillance among patients with complete mole.

MATERIALS AND METHODS: A cohort of patients with sonographic diagnosis of complete hydatidiform mole and managed with suction curettage in the same institution were prospectively followed up after evacuation. The pre- and postmolar evacuation surveillance period was at days 1, 7, 14, 21, 28, and 35. Monitoring of serum β-hCG levels was based on the standard regression curve. For Doppler ultrasound parameters, monitoring of the systolic/diastolic (S/D) ratio, pulsatility index (PI), resistance index (RI), and peak systolic velocity (PSV) was based on its relationship with its serum β-hCG levels. The ultrasound images generated were archived and reviewed by the authors. Descriptive and inferential statistics were utilized to analyze median differences. For the correlation of uterine artery Doppler flow parameters, analysis for the test of difference used Pearson correlation and multiple linear regression analysis for the odds ratio.

RESULTS: Sixteen of the 23 enrolled patients completed the protocol (16 of 23, 69.50%). A majority had spontaneous remission (13; 81%) while 3 cases (19%) presented increasing and plateauing β-hCG levels. The pre- and post evacuation median β-hCG levels showed a significant decrease ($P = 0.001$). As post evacuation β-hCG levels decreased, PSV also decreased ($r = 0.478$, $P = 0.061$) while Doppler parameters, RI, PI, and S/D ratio increased. However, when post evacuation β-hCG levels rose or plateaued, Doppler parameters decreased. These changes had statistical correlation (all $P < 0.05$). Moreover, the magnitude of the relationship for β-hCG and Doppler parameters was moderate and ranged from 0.524 to 0.581. Among the Doppler parameters, the S/D ratio and RI of the right uterine artery strongly predicted a rise in β-hCG levels. The odds ratio of predicting increased β-hCG levels and risk of gestational trophoblastic neoplasia by the right S/D ratio were − 2683.67 (confidence interval [CI] = −271.692–5095.655; $P = 0.034$) and by the right RI − 66,193.34 (CI = −161,818.107–29,431.433; $P = 0.046$). Notably, Doppler parameter changes appeared early at day 14 up to day 35 and before the appearance of abnormal β-hCG regression patterns.

CONCLUSION: There is a strong correlation between uterine artery Doppler flow changes and β-hCG levels during postmolar evacuation surveillance. The inverse relationship of the S/D ratio, PI and RI,

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and β-hCG regression patterns confirms spontaneous remission of the disease. For patients with abnormal β-hCG patterns, this relationship is altered. The Doppler changes become erratic, unpredictable, and significantly decreased. These changes were detected as early as 2 weeks post evacuation. Thus, the use of ultrasound as an adjunct to β-hCG post evacuation surveillance can predict abnormal β-hCG regression patterns and identify patients at risk of developing postmolar gestational trophoblastic neoplasia (PMGTN).

Keywords:

Beta-human chorionic gonadotropin regression curve, complete hydatidiform mole, Doppler flow velocimetry parameters, postmolar evacuation surveillance, postmolar gestational trophoblastic neoplasia

Introduction

Gestational trophoblastic diseases (GTDs) present a spectrum of benign and malignant entities arising from trophoblastic tissues. It has a wide geographic variation with the incidence of hydatidiform mole varying between 0.57 and 2/1000 pregnancies[1] The Philippines has a reported incidence for hydatidiform mole of 2.4/1000 pregnancies in 2018. The demographic profile of a Filipino patient with hydatidiform mole were mean age of 28.3 years (15–53 years), mean age of gestation on diagnosis of 14.5 weeks (6–24 weeks), and mean baseline serum β-human chorionic gonadotropin (hCG) value of >100,000 mIU/ml (621–>100,000).[2]

Post evacuation surveillance using serial measurements of β-hCG is the standard method for monitoring residual trophoblastic tissues. An increase or plateau of the β-hCG curve allows early recognition of patients with persistent disease prompting evaluation for gestational trophoblastic neoplasia (GTN).[3] Further, spontaneous regression of β-hCG levels is not expected with persistent viable trophoblastic tissues and no definite time is necessary for normalizing serum β-hCG among patients with spontaneous regression.[4-6] Thus, a baseline β-hCG measurement is obtained within 48 h Post evacuation and compared every 1–2 weeks until it declines and is undetectable.[7] Once serum β-hCG is normalized after 56 days, monthly serum β-hCG measurements are continued for 6 months. During the follow-up period, contraception is advised, and low-dose combined oral contraceptive pills are the preferred method. If β-hCG levels increase, or a fall of <10%, or is present for more than 6 months, the patient is suspected to have persistent viable trophoblastic tissues.[8] A diagnosis of postmolar gestational trophoblastic neoplasia (PMGTN) is by β-hCG surveillance without symptoms. The 2021 FIGO Cancer Report provides the following criteria for diagnosis of PMGTN: (1) When the plateau of β-hCG lasts for four measurements over a period of 3 weeks of longer; that is days 1, 7, and 14; (2) When there is a rise in β-hCG for three consecutive weekly measurements over at least a period of 2 weeks or more; days 1, 7, and 14; and (3) If there is a histologic diagnosis of choriocarcinoma.[9]

Angiogenesis is the hallmark of tumorigenesis while hypervascularity is for GTN. Studies on angiogenesis are by immunostaining and *ex vivo*, wherein biopsies are required but may not represent the whole tumor or do not provide the functional assessment of the neovascularization.[10] Ultrasound is the imaging of choice for the initial diagnosis of GTD. With the availability of high-resolution transvaginal ultrasound, evaluation of angiogenesis *in vivo* of the tumor's vascularity and the host organ's blood supply is made easier. Detection rates are between 80% and 95% for complete molar pregnancy.[11,12] Doppler ultrasound is noninvasive and available. It can evaluate and measure blood flow using three modalities: color flow imaging for blood flow direction based on frequency change; power Doppler for amplitude changes specially to slow frequency but not on direction; and spectral Doppler for functional assessment of the circulation by calculating velocities based on the blood flow waveforms.[13] In molar pregnancy, uterine artery Doppler flow velocimetry appears as a high-velocity and low-impedance waveform brought about by the arterial invasion of abnormally proliferating trophoblastic cells.[14] In an invasive myometrial mass, color Doppler illustrates neovascularization as a chaotic abundant vascularity with color aliasing and loss of vascular differentiation. Doppler velocimetry of its uterine artery will demonstrate a high velocity and low impedance flow.[15,16] Quantifying vascular impedance uses the uterine artery pulsatility index (PI) and resistance index (RI). A low PI and RI ratio quantifies a low resistance flow and vice versa. Some studies suggested cutoff values for RI <0.4 and PI <1.5.[17] Aside from investigating abnormal vascular patterns, Doppler ultrasound can detect an invasive disease based on the extension of abnormal vascularity into the myometrium and can predict late or slow response or resistance to chemotherapy in low-risk trophoblastic neoplasia. Doppler findings can be an ancillary tool with β-hCG in the diagnosis of GTN.[18-22] In a prospective cohort study of 246 patients who underwent pre- and post evacuation Doppler measurements, patients who progressed to PMGTN had lower PI (odds ratio of 13.9–30.5) while patients in spontaneous remission had increased post evacuation PI and systolic/diastolic (S/D) ratio.

A pre evacuation PI of <1.38 (77% sensitivity and 82% specificity) and Post evacuation PI of < 1.77 (79% sensitivity and 86% specificity) can predict GTN. A normal uterine artery peak systolic velocity (PSV) and end-diastolic flow velocities after a clinical remission implies the absence of viable trophoblastic tissues.[22] However, more evidence is needed to include Doppler ultrasound in the Post evacuation surveillance protocol to complement with serum β-hCG levels in predicting patients at risk of developing GTN.

The aim of the study is to correlate uterine artery Doppler ultrasound parameters with serum β-hCG during Post evacuation surveillance among patients with complete mole.

Specific objectives

1. To determine the sociodemographic profile of participants with complete hydatidiform mole based on age, gravidity, parity, gestational age, uterine size, and the presence or absence of theca lutein cysts
2. To compare pre- and post evacuation measurements of uterine artery Doppler flow velocimetry and changes and blood levels of β-hCG
3. To correlate the changes of uterine Doppler flow velocimetry indices with serum β-hCG level
4. To determine the odds ratio of uterine Doppler flow velocimetry indices to β-hCG level adjusted for clinical variables such as age, gestational age, uterine size, and theca lutein cysts.

Materials and Methods

This study was approved by the Cluster Ethics Research Committee bearing CERC Protocol Number P18091601.

A prospective cohort study design was conducted among patients diagnosed with complete hydatidiform mole and managed with suction curettage in the same institution. Patients aged 18–50 years old, with a sonographic diagnosis of complete hydatidiform mole, with or without theca lutein cysts, underwent suction evacuation in the same institution, with baseline serum β-hCG, and consented to undergo Doppler ultrasound and serial serum β-hCG monitoring during Post evacuation surveillance days 1, 7, 14, 21, 28, and 35 were included in the study. The surveillance schedule followed the FIGO criteria for diagnosis of PMGTN.[9] Patients below 18 years old or managed with surgical removal of the uterus or unable to complete the Post evacuation surveillance were excluded from the study. Upon admission, a data collection form recorded the age, parity, gestational age, pre evacuation β-hCG level, uterine size, the presence or absence of theca lutein cysts, serum β-hCG levels, and Doppler ultrasound parameters.

All ultrasound procedures were performed using GE Voluson E8 and S6, 5–7 MHz three-dimensional endovaginal probe. The author (GCP) performed and recorded the grayscale images and Doppler ultrasound videos. These recordings and measurements were reviewed and validated by the corresponding author (VMD). An interobserver variation between measurements of ≤5% was acceptable. The participant was placed in a dorsal lithotomy position. The sheathed probe was inserted into the vagina and placed at the anterior vaginal fornix to acquire a sagittal plane of the cervix and uterus. Lateral sweeping of the probe was done to locate the ascending branch of the uterine artery either at the level of the internal os, at the cervical corporeal junction, or at the point closest to the internal os. After demonstrating the vessel on the grayscale and color flow, pulsed wave Doppler was applied with the following settings: 2 mm sampling gate, angle of insonation between 0° and 15°, pulse repetition frequency at 1.8 or over, color gain −2, and reproduced 4–6 consecutive similar waveforms. The PSV, PI, RI, and S/D ratio Doppler parameters were automatically calculated [Figure 1]. All images, measurements, and video clips were archived for review. Blood test for serum β-hCG was done on the same setting. The same process was conducted on postevacuation days 1, 7, 14, 21, 28, and 35. Sampling was nonrandomized and based on the number of patients with complete molar pregnancy seen at the ultrasound unit over a 6-month period. The level of significance was set at 5% margin error and 95% confidence interval (CI). For the clinical characteristics, descriptive statistics such as median (minimum–maximum) to scale variables, frequency, and percentage for nominal variables. An inferential statistics Wilcoxon sign test (two-tailed) was utilized for statistical analysis of the median differences pre- and post evacuation. For the correlation of changes

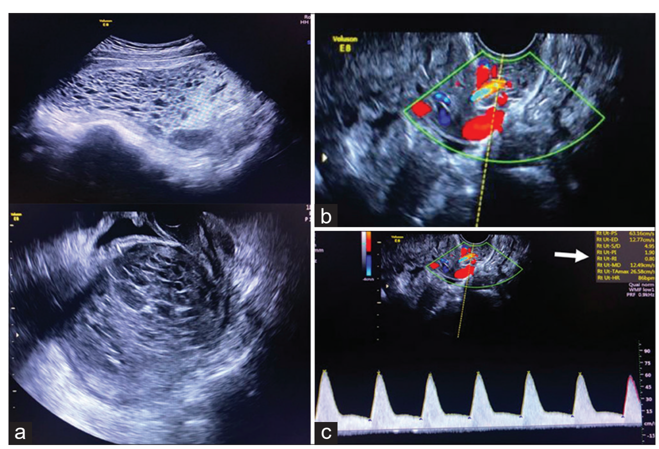

Figure 1: Ultrasound images. (a) Grayscale images of a complete hydatidiform mole showing multiple irregularly-shaped cystic spaces within the uterine cavity; (b) Color flow imaging of the ascending branch of both uterine arteries located at the uterine isthmus; (c) Doppler flow velocimetry of the uterine artery shows a high resistance and low Impedance waveform. White solid arrow points to the system-generated Doppler flow indices

in uterine artery Doppler flow velocimetry indices with serum β-hCG, Pearson product-moment correlation was used but limited to four variables that are normally distributed except for β-hCG, right RI, and left PI. Multiple linear regression analysis was used but with limitations on the multicollinearity test to determine the odds ratio of uterine Doppler flow velocimetry indices to β-hCG level adjusted for clinical variables.

Results

Twenty-three patients with complete hydatidiform mole were enrolled and 16 (69.5%) completed the protocol. Seven (30.5%) patients withdrew on days 14 and 21. Table 1 presents the clinical characteristics of the 23 enrolled patients. The median age in years was 24.0 (18.0–36.0), gravida 2.0 (0–3.0), parity 1.0 (1.0–3.0), and gestational age of 13.5 (6.0–24.0) weeks. Most patients (19/23; 82.6%) presented with uterine enlargement and without theca lutein cysts (19/23; 82.6%), while the remainder had small uteri (4/23; 17.4%), with > 6 cm-size theca lutein cysts (4/23; 17.4%). The median pre treatment Doppler flow parameters and β-hCG levels of the right and left uterine arteries are shown in Table 2. Both arteries showed an increase in post evacuation Doppler flow parameters and were statistically significant (right PI, $P = 0.006$; RI, $P = 0.041$; and S/D ratio, $P = 0.027$ and left PI, $P = 0.002$; RI, $P = 0.008$; and S/D ratio, $P = 0.001$). Notable was the statistical difference observed with the decreasing PSV values (right, $P = 0.001$ and left, $P = 0.003$) and β-hCG levels (pre evacuation 279,400 mIU/ml and post evacuation 42.00 mIU/ml, $P = 0.001$). Table 3 presents the correlation between uterine artery Doppler flow indices and β-hCG. Except for β-hCG and RI, all values were normally distributed. A significant correlation was noted on both uterine arteries for RI (right, $r = -0.525$, $P = 0.037$ and left, $r = -0.524$; $P = 0.037$) and PI (right, $r = -0.673$ and $P = 0.004$; left, $r = -0.695$; $P = 0.003$). There is an inverse relationship was observed between Doppler parameters and β-hCG levels. The uterine artery S/D ratio, PI, and RI increase while serum β-hCG levels decrease. This difference was evident on the left uterine artery ($P = 0.018$). The magnitude of the relationship across all Doppler flow parameters to serum β-hCG was moderate and ranged from 0.524 to 0.581. However, PSV showed the opposite. PSV levels mirrored the β-hCG levels. As β-hCG levels decreased, PSV levels decreased and showed strong correlation ($r = 0.478$; $P = 0.061$). Table 4 presents a multiple linear regression analysis on the usefulness of uterine artery Doppler velocimetry as a predictor of GTN and serum β-hCG levels when adjusted for age, gestational age, uterine size, and theca lutein cysts. Two out of the eight Doppler parameters showed significant results in predicting decreasing serum β-hCG levels, the right artery S/D ratio, and right artery RI. The odds ratio of predicting GTN for the right S/D

Table 1: Clinical characteristics of patients enrolled (*n*=23)

Characteristics	Median
Age years (median)	24.0 (18.0–36.0)
Gravidity (median)	2.0 (0–3.0)
Parity (median)	1.0 (1.0–3.0)
Gestational age (median)	13.5 (6.0–24.0)
Uterine size>gestational age	
< Gestational age	4 (17.3)
> Gestational age	19 (82.6)
Theca lutein cyst >6 cm	
No	19 (82.6)
>6 cm	3 (13.0)
<6 cm	1 (4.0)

Table 2: Median pre- and post evacuation measurements of both uterine arteries based on Doppler flow velocimetry indices and beta-human chorionic gonadotropin levels until day 35 (*n*=16)

Doppler indices	Pre	Post	*P*
Right uterine artery			
PSV	81.84 (40.06–107.57)	33.90 (13.14–58.22)	0.001†
PI	1.65 (0.87–2.90)	2.87 (0.69–3.38)	0.006†
RI	0.75 (0.55–1.01)	0.88 (0.47–0.92)	0.041†
SD ratio	4.02 (2.21–37.52)	8.32 (1.90–12.07)	0.027†
Left uterine artery			
PSV	71.50 (35.62–151.02)	29.89 (18.22–63.06)	0.003†
PI	1.35 (0.86–2.83)	2.68 (0.60–3.86)	0.002†
RI	0.69 (0.55–0.91)	0.86 (0.43–0.95)	0.008†
SD ratio	3.22 (2.23–11.64)	7.06 (1.76–20.12)	0.001†
β-hCG levels (mUI/mL)	279,400 (44,757–279,400)	42.00 (10.10–830.96)	0.001†

†Significant at $P<0.05$, Wilcoxon.[29] Median (minimum-maximum). β-hCG: Beta-human chorionic gonadotropin, SD: Systolic/diastolic, PSV: Peak systolic velocity, RI: Resistance index, PI: Pulsatility index

Table 3: Correlation of uterine artery Doppler flow indices and beta-human chorionic gonadotropin (*n*=16)

β-hCG	Right uterine artery				Left uterine artery			
	PSV	SD	PI	RI	PSV	SD	PI	RI
r	0.478	−0.357	−0.673**	−0.525*	0.229	−0.581*	−0.695**	−0.524*
P	0.061	0.174	0.004	0.037†	0.394	0.018†	0.003†	0.037†
n	16	16	16	16	16	16	16	16

†Significant at $P<0.05$. *Significant at 5% level of significance. **Highly significant at 1% level of significance. Values are normally distributed except for β-HCG, RI right and RI left. β-hCG: Beta-human chorionic gonadotropin, RI: Resistance index, PI: Pulsatility index, SD: Systolic/diastolic, PSV: Peak systolic velocity

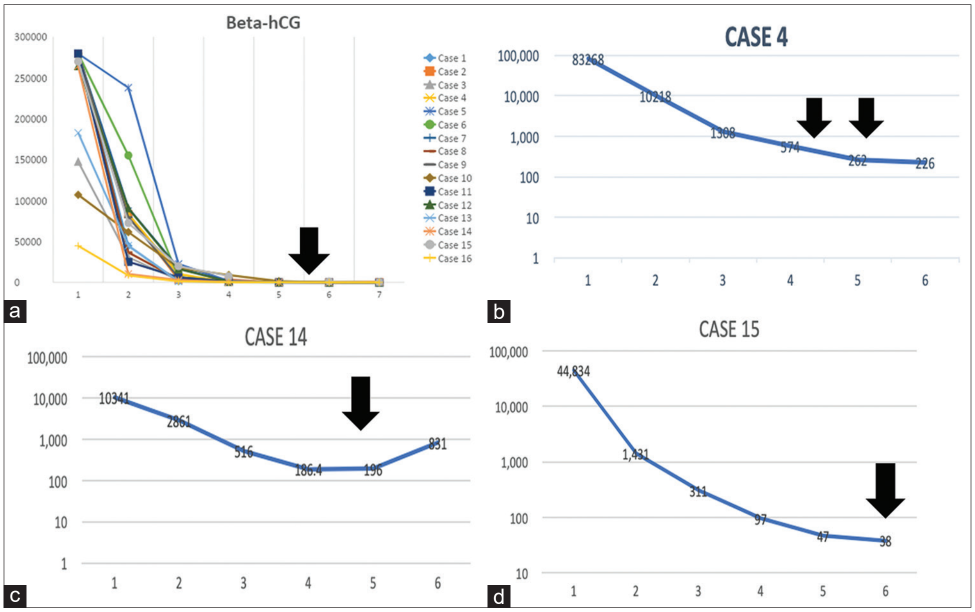

Figure 2: Beta-human chorionic gonadotropin (β-hCG) regression patterns. (a) thirteen of the 16 cases (69.5%) followed the spontaneous B-hCG regression curve. (b-d) the three cases with atypical B-hCG patterns until day 35; the solid black arrow points to the changes. (b) Case 4 plateauing on day 28 and 35 (c) Case 14 plateauing on days 21 and 28 and rising on day 25. (d) Case 15, B-hCG levels are still detected on day 35

Table 4: Multiple linear regression of the usefulness of each uterine Doppler flow velocimetry parameters as a predictor of gestational trophoblastic neoplasia adjusted for age, gestational age, size uterus, and theca lutein cysts (average median from pre- to post-evacuation surveillance day 35)

Index_Side	OR	P
Constant	63,175.502	0.005
PSV_Right	73.790 (−243.110–95.529)	0.337
SD_Right	−2683.674 (−271.692–5095.655)	0.034†
RI_Right	−66,193.337 (−161,818.107–29,431.433)	0.046†
PI_Right	−1552.541 (−7144.315–4039.232)	0.532
PSV_Left	−27.107 (−290.659–236.446)	0.815
SD_Left	−674.374 (−2103.447–754.698)	0.301
RI_Left	−25,668.090 (−115,971.504–64,635.324)	0.523
PI_Left	4588.070 (−3945.361–13,121.500)	0.244

†Significant at $P<0.05$. $R=0.907$, $R^2=0.823$, Adjusted $R^2=-0.621$; $F=4.070$, $P=0.040$. OR: Odds ratio, RI: Resistance index, PI: Pulsatility index, SD: Systolic/diastolic, PSV: Peak systolic velocity

ratio was − 2683.674 (CI − 271.692–5095.655; P = 0.034) and for the right RI was − 66,193.337 (CI − 161,818.107–29,431.433; P = 0.046). A decrease in the right S/D ratio and right RI can predict a rise in the serum β-hCG levels by 2683.674 and 66,193.337, respectively.

Discussion

Persistence of trophoblastic activity after molar evacuation begins as microinvasive moles and transforms the uterus into a low-impedance organ causing uterine hypercompression. The intratumoral blood flow of the vesicular tissues changes the uterine circulation and flow meter of the uterine arteries and its branches. A high PSV ratio and low S/D ratio, PI, and RI represent high uterine blood flow velocity and low impedance flow. Such features reflect neovascularization in tumors. As for β-hCG levels, spontaneous regression occurs in 49–99 days and disappears within 98–278 days. In uncomplicated hydatidiform moles, spontaneous regression is 4–12 weeks.[6,23] To diagnose PMGTN, 2021 FIGO criteria require at least a 2-week increase or plateau of β-hCG levels. This puts Doppler ultrasound at an advantage since it can detect abnormal vascular changes in invasive moles as early as 2 weeks post evacuation, before the appearance of uterine lesions and hypervascularity, or before abnormal changes in β-hCG regressive curves are detected.[22]

The clinical profile of the 16 cases is the same as Cagayan's study (2010). The relationship between β-hCG levels and the Doppler flow parameters is also observed. In Figure 2, the majority of the cases showed spontaneous regression of β-hCG levels within days 7 and 21. By day 35, end of the surveillance period, 13 cases presented with undetected β-hCG levels and 3 cases showed persistent β-hCG levels. In case 4, β-hCG plateaus at day 28 and 35, case 14 had β-hCG plateaus at day 21 and 28 with a rise at day 35, and in case 15, β-hCG levels were still detected at day 35. These abnormal regression patterns reflect the persistence of trophoblastic activity but are incomplete for a diagnosis of PMGTN. Figure 3 demonstrates the inverse relationship between the median levels of β-hCG levels and the uterine artery PI, RI, and S/D ratio while PSV follows the β-hCG levels. Figure 4 shows the erratic and unpredictable behavior of the Doppler flow parameters of cases 4, 14, and 15 during the surveillance period. Notable is case 14, the PI, RI,

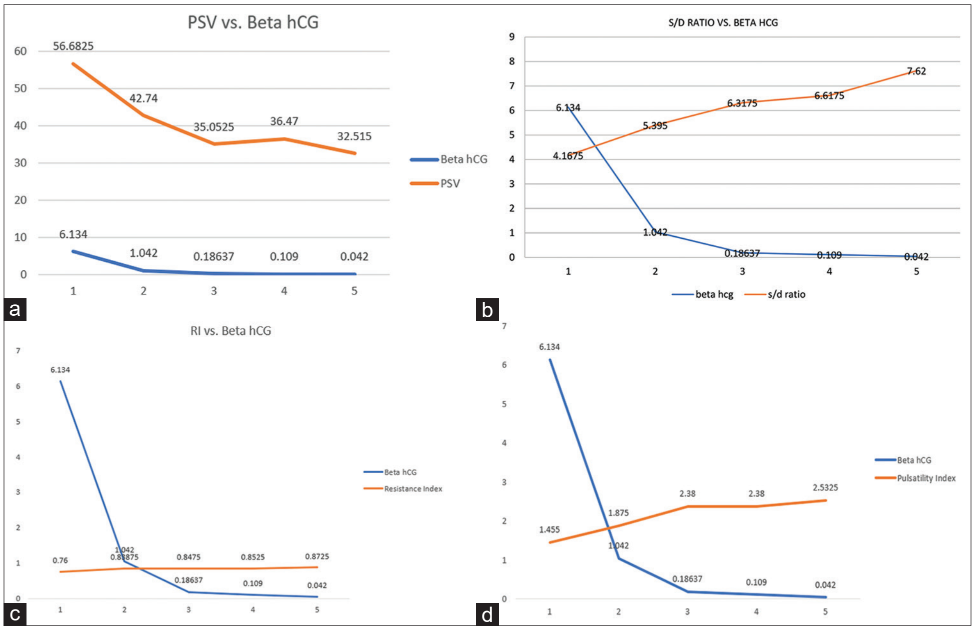

Figure 3: Relationship patterns between Doppler flow (orange line) and beta-human chorionic gonadotropin regression curves (blue line): Peak systolic velocity levels mirror β-hCG levels demonstrating a direct relationship (a). Systolic/diastolic (S/D) ratio, resistance index, and pulsatility index have an inverse relationship with β-hCG levels. As β-hCG levels decrease, S/D ratio (b); Resistance index (c); and Pulsatility index (d) increase. β-hCG: Beta-human chorionic gonadotropin, PSV: Peak systolic velocity, S/D ratio: Systolic/diastolic ratio, RI: Resistance index

and S/D ratios were low as early as day 7 and persisted until day 35. As for PSV levels, there were more spikes than lows which mirrors the abnormal β-hCG levels. Still on day 35, a hypoechogenic heterogenous irregular endometrial-myometrial solid uterine lesion measuring 52.5 mm × 31.1 mm × 54.7 mm (volume: 47.69 cm^3) was detected on ultrasound [Figure 5]. These changes were captured early by ultrasonography. Doppler velocimetry can predict GTN based on the presence of a uterine tumor and hypervascularity, higher uterine artery PSV, and lower uterine artery RI and PI.[22] Thus, the ultrasound findings put case 14 at high risk of having PMGTN.

Related studies show uterine artery PI as the Doppler parameter strongly associated with the risk of PMGTN.[22,24-27] The proposed cut-off PI values of pre evacuation of </= 1.38 yielded 77% sensitivity and 82% specificity and post evacuation PI </= 1.77 were similar at 79% sensitivity and 82% specificity in predicting GTN.[21] Our results showed higher Doppler values with convincing pre- and post evacuation differences. The post evacuation S/D ratio, PI, and RI were high because the majority of the cases were in spontaneous remission. Individually, case 14 had post evacuation PI values lower than the cutoff value of ≤1.77 which is predictive of PMGTN. Using multiple regression, four prognostic variables were selected and adjusted to determine the usefulness of these Doppler parameters to β-hCG levels in predicting GTN. The four variables were maternal age, gestational age, uterine size, and theca lutein cysts. Two Doppler parameters, right uterine artery S/D ratio and right uterine artery RI, can predict increasing β-hCG levels by an odds ratio of −2683.674 (P = 0.034) and −66,193.337 (P = 0.046), respectively. Thus, a low right uterine artery S/D ratio and RI adjusted by maternal age, gestational age, uterine size, and theca lutein cysts have higher odds at predicting a rise in β-hCG levels and identifying patients at risk of PMGTN.

The results of this study support the concept of Doppler ultrasound's importance in the diagnosis and treatment of GTDs. In fact, the 2022 Clinical Practice Guidelines for GTN and for hydatidiform mole by the Philippine Society for the Study of Trophoblastic Diseases, Inc. strongly recommend the use of transvaginal ultrasound with Doppler as an adjunct in the diagnosis of GTN and in monitoring response to treatment in patients with GTN. Studies have shown Doppler ultrasound's sensitivity to vascular resistance can be a useful predictor of response to chemotherapy.[28]

Limitation of the study

The small sample size and short surveillance period of 35 days limited the study from demonstrating abnormal β-hCG regression curves. It also restricted the researchers from making a diagnosis of GTN based on the 2021 FIGO criteria. With only three cases showing abnormal β-hCG levels, data were inadequate to provide certainty of evidence on the use of Doppler ultrasound in identifying patients at risk for PMGTN. This is a result of the small study population. However, case 14 provided tangible proof that changes in Doppler ultrasound parameters do occur. In fact, these changes were detected earlier than

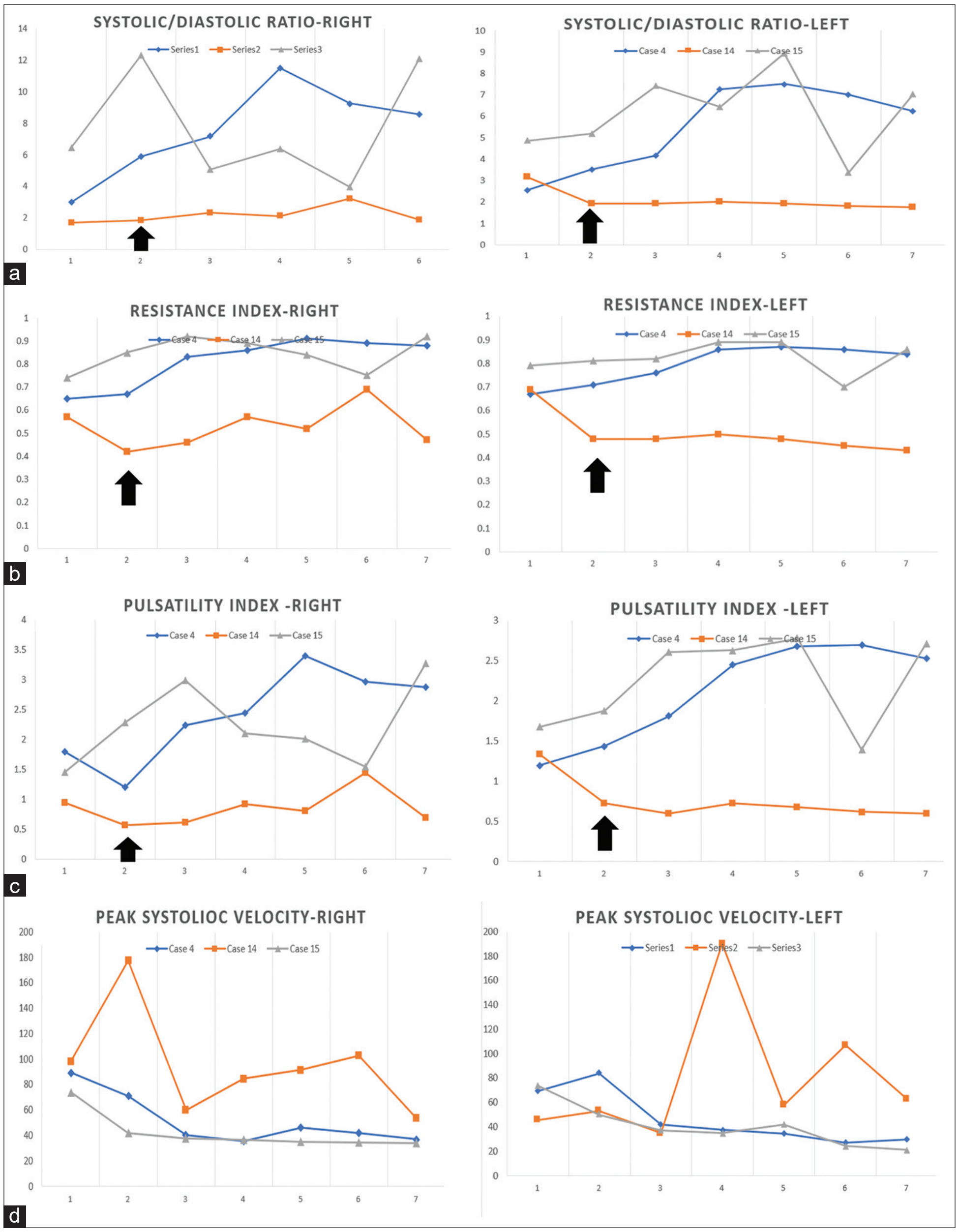

Figure 4: Erratic and Unpredictable Uterine Doppler Flow Patterns of the 3 cases with atypical b-hCG regression patterns. Graphs A-C demonstrate the low levels of S/D ratio, PI, and RI specifically on Case 14 (orange line), detected early on Day 7 as pointed by the black solid arrow (↑) and persisted until Day 35. Graph D shows the PSV pattern mirrors the spikes of the b-hCG levels. S/D ratio: Systolic Diastolic Ratio, RI: Resistance Index, PI: Pulsatility Index, PSV: Peak Systolic Velocity

the abnormal β-hCG regression curve required by the FIGO criteria for diagnosis of GTN. Thus, a relationship does exist between Doppler ultrasound and β-hCG regression levels.

Recommendation

Even with the study's limitations, the results, and findings of case 14 warrant further investigation. Population-based studies of molar pregnancies on Doppler ultrasound in complementary with β-hCG monitoring during postevacuation surveillance is recommended. This is to provide quality evidence on the extent of Doppler ultrasound in predicting patients at risk of developing GTN and response to treatment.

Conclusion

There is a strong correlation between changes in uterine artery Doppler blood flow velocity and β-hCG levels during postmolar surveillance. For those with spontaneous remissions, an inverse relationship is established with Doppler parameters S/D ratio, RI, and PI while PSV is directly proportional to the β-hCG regression curve. A normal Doppler flow study and undetectable β-hCG levels for more than 2 consecutive weeks are considered complete treatment.[28] Notably, low Doppler

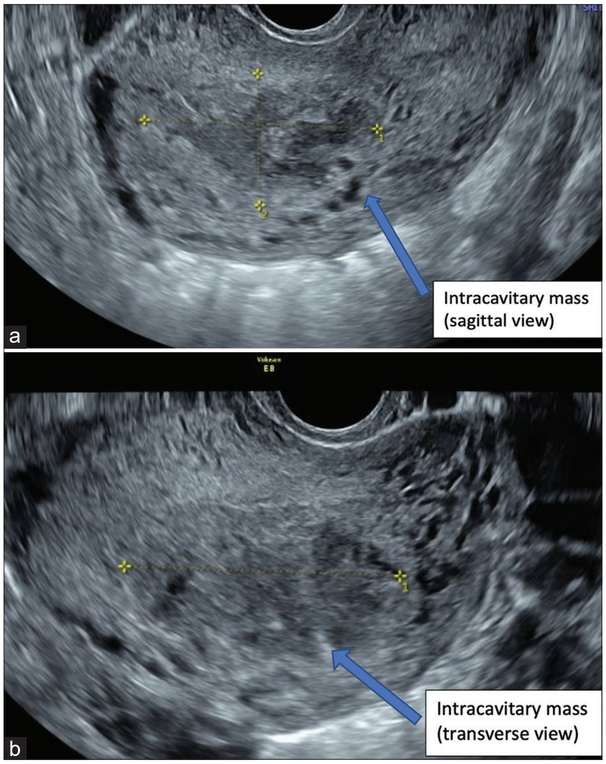

Figure 5: Case 14 was the sole study participant with a uterine mass detected by ultrasound on Day 35. The endometrium is indistinct on (a) sagittal and (b) transverse planes. The lesion is heterogenous irregular and solid measuring 52.5 mm x 31.1 mm x 54.7 mm with moderate vascularity

indices are detected as early as day 14 postevacuation and before increasing/plateauing β-hCG levels. This feature supports the potential role of Doppler ultrasound in identifying patients at risk in developing GTN.

Authorship contributions

1. Geraldine Posecion involved in the conceptualization, methodology, formal analysis, investigation, resources, data curation, writing-original draft, visualization, project administration, and funding acquisition.
2. Veronica Deniega involved in the conceptualization, methodology, validation, investigation, writing-review editing, visualization, supervision.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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