Uterine Artery Doppler Blood flow in Cases of Hydatidiform Mole and its Correlation with β-hCG

Neda Salih Amin, F.R.C.S. (Ed)* **Rasha Najah Yassen, F.I.C.M.S.****
Haider Fa'ak Abd-EL-Kareem F.I.C.M.S. ***
Ahmed Abd Al-Jabbar Al-Sabbagh F.I.C.M.S. (Radiology)****

Abstract

Background: Gestational trophoblastic disease (GTD) is an uncommon complication of pregnancy, worldwide the incidence of GTD varies reportedly between 0.5 & 0.8 cases per 1000 live births. β-hCG has been used as standard tool for monitoring the biological activity of trophoblastic diseases and as a tumour marker. The abundant vascular supply of the tumour makes Colour Doppler Ultrasound a potentially useful tool to study the correlation of tumour's blood flow and its clinical behaviour.

Objective: To study the changes in the Doppler blood flow velocity of the uterine artery, the correlation between resistance indices & β-hCG level before and after evacuation of molar pregnancy as well as the value of Doppler flow in assessing the course of the disease.

Patients and Methods: A-longitudinal study was conducted in AL-YARMOUK Teaching Hospital, Department of Obstetrics & Gynaecology, from Jan.2006 through Jan.2007.

Twenty five cases of vesicular mole entered the study and were assessed before and after evacuation of the uterus by measuring serum β-hCG level and finding its relation with changes in the blood flow of the uterine artery using Doppler indices namely Systolic/ Diastolic (S/D), Resistance Index (RI), and Pusatility Index (PI).

Results: Twenty two out of twenty five cases showed continuous decrease of their β-hCG serum level from pre-evacuation value of 1724.23 + 997.32 IU/L until it reached a value of 74.68 + 43.96 IU/L in the 6th week after evacuation.(P value = 0.0001), The Twenty two cases also showed continuous increase of all Doppler indices from pre-evacuation level to 6th week after evacuation as shown below:

S/D pre-evacuation = 2.25 + 0.77 IU/L reached 10.12 + 0.79 IU/L in the 6th week post-evacuation.

PI pre-evacuation =0.96 + 0.26 IU/L reached 4.1 + 1.08 IU/L in the 6th week post-evacuation.

RI pre-evacuation =0.47 + 0.07 IU/L reached 0.95 + 0.08 IU/L in the 6th week post-evacuation.

Two patients showed no consistent decrease of β-hCG serum level with plateuing of all Doppler indices for which Dilatation & Curettage (D&C) revealed Persistent Gestational Trophobastic Disease (PGTD).

One patient showed significant increase of β-hCG serum level in the 6th week post-evacuation with drop of all Doppler indices.

There was significant correlation (P value < 0.05) between β-hCG serum levels and Doppler indices throughout the course of follow-up:

β-hCG & S/D(r) = - 0.778, β-hCG & RI(r) = - 0.581, β-hCG & PI(r) = - 0.483,

Conclusion: Finding such a significant correlation between β-hCG serum level and Doppler indices suggest that colour Doppler may be used to predict the course of the disease and define its course.

Keywords: Gestational Trophoblastic Disease (GTD), molar pregnancy, β-hCG level, Doppler indices.

Introduction

Gestational trophoblastic disease (GTD) is an uncommon complication of pregnancy. The term GTD describes a group of interrelated diseases including: Complete Hydatidiform Mole (CHM), Partial Hydatidiform Mole (PHM), Choriocarcinoma (CC) and Placental Site Trophoblastic Tumour (PSTT). Worldwide the incidence of GTD varies reportedly between 0.5 and 0.8 cases per 1000 live births. [1] The incidence of Hydatidiform mole is well known to be highest in South East Asia with rates ranging 1-2 / 1000 pregnancies in Japan and China. [2]

The history and management of trophoblastic diseases can be considered as one of success stories of modern medicine as the majority if not all the women are potentially curable once prompt diagnosis and treatment commence early enough. [3]

Molar pregnancy may presents with: vaginal bleeding(89-97 %), uterine enlargement larger than date (40-50 %),Hyperemesis gravidarum (15-25 %), Theca lutein cyst (10- 14 %) , absent fetal heart tones in CHM and other clinical feature **s**uch as anemia, pre-eclampsia, hyperthyroidism, pulmonary insufficiency, metastatic disease seen less often except in countries with less developed health care system. [4] Molar pregnancy diagnosis depends on clinical finding, maternal serum β-hCG level and ultrasound examination. [5] Molar pregnancy management is by suction evacuation method of choice [1], hysterectomy is an option for good surgical candidates not desirous for further pregnancy and elder women[6] and prophylactic chemotherapy for patients with high risk for malignancy (greater than 35years, previous hydatidiform mole, poor follow-up). [6]

Human Chorionic Gonadotrophine (hCG) is a glycoprotein that contains galactose hexosamine. It is produced by syncytiotrophoblast. Like pituitary glycoprotein hormones it is made up of α and β subunits. hCG α subunit is identical to α subunit of LH, FSH, and TSH. Molecular weight of α subunit is 18 000 and of β subunit is 28 000. hCG is primarily leutinizing and leuteotropic and has little FSH activity. It can be measured using radioimmunoassay (RIA), fluroimmunoassay (FIA) and enzyme immunoassay (ELISA) to sensitive levels below 5 mIU / ml. It can be detected in blood as early as 6 days after conception. Its presence in urine in early pregnancy is the basis for various

laboratory tests for pregnancy and it can be detected in urine as early as 14 days after conception. It appears to act on the same receptors as LH. hCG is not absolutely specific for pregnancy. Small amounts are secreted by variety of gastrointestinal and other tumours. It also appears that fetal liver and kidneys normally produced small amounts of hCG. [7] The laboratory assays based on antibody recognition of hCG β-subunit and typically measure both free β-subunit and intact hCG. [5] hCG regulates the differentiation of cytotrophoblasts via its receptors and thus its own synthesis. Higher concentrations of hCG receptor mRNA protein are found in hyperplastic trophoblast and hCG cannot regulate its synthesis under this condition. It has been found that concentration of intact hCG and free β-hCG are high in all categories of CHM and PHM. The placental overgrowth could explain the increased maternal serum hCG concentration. In CHM intact hCG and free β-hCG subunits concentration are increased and they are higher than PHM. [8]

The incidence of malignant disease following hydatidiform mole is about 20-30 % so that close follow-up and serial hCG level is essential for every patient. [6]

Following evacuation of hydatidiform mole the patient should have: gynaecological examination done one week after evacuation for uterine size, adnexal mass and unless symptoms develops examination should be repeated at 4 weeks interval[6] ,serial serum β-hCG level at weekly interval until it declines to non detectable levels on 3 successive assays.

The average disappearance time of serum β-hCG after CHM is 99.3 days and after PHM is 68.9 days. It is recommended NOT to start chemotherapy for Persistent Gestational Trophoblastic Diseases (PGTD) before 100 days after CHM evacuation provided steady downward course of serum β-hCG levels. [9]

Most critical time for observation is 4-6 weeks post-evacuation and about 70 % would achieve normal hCG levels within 60 days post-evacuation.

Current data suggest that 15 % of patients demonstrate a continuous decline in titres without any treatment. 15 % of the patients would demonstrate increasing titres at 60 days post-evacuation showing rising or plateau levels. Nearly half of them would have Invasive mole and half of them would have Choriocarcinoma. [6]

It is convenient to ask patients to avoid further pregnancy for 6-12 months following molar pregnancy to enable efficient hCG follow-up. [1]

Oral contraceptives are widely used as highly effective method during the first 6-12 months. In vitro studies have reported inhibitory or no effect on trophoblastic cells replications on hCG secretion. [10]

Up to 20 % of patients, trophoblastic disease persists as evidenced by continuing clinical symptoms (particularly vaginal bleeding) and / or elevation of hCG levels. Excessive uterine size, marked elevation of hCG levels and prominent theca lutein cysts are the main predicting factors. [1, 2]

In practice only two indices classes are used: those related to the degree of diastolic flow and others related to spectral broadening. The variation in time of the maximum velocity displayed in spectrogram is commonly used as a source of data for the rivation of an index. Mean velocity waveform is also employed and it is used together with the vessel cross-sectional area to calculates blood flow. Indices are therefore defined involving ratios of velocities and the measured index is independent of beam angle. [11, 12]

There is a significant increase in myometrial and endometrial blood flow as evidenced by colour Doppler in all trophoblastic tumours. This is usually more marked in more aggressive tumours, thus trophobalstic neoplasia is particularly suitable for blood flow study by colour Doppler ultrasound because of the intrinsic characteristics of trophoblast to form blood lacunae by destroying uterine vasculature and formation of low resistance blood vessels. [11]

Patients and Methods

This longitudinal study was carried out in AL-YARMOUK Teaching Hospital in the Department of Obstetrics and Gynaecology during the period from Jan.2006 to Jan.2007.

Twenty five women with vesicular mole (24 cases were Complete Hydatidiform Mole and one Partial Hydatidiform Mole) were included in this study.

The patients were recruited from out-patient clinic and hospital admissions.

An informed verbal consent was obtained from all women included in this study.

A full medical, obstetric and gynaecological history was obtained from each candidate with special attention paid for age, reproductive factors, blood group of the patient and her husband as well as family history of the condition.

The patients were evaluated the day before evacuation of the uterus. This evaluation included:

1. Clinical assessment involving general, abdominal and bimanual pelvic examination.
2. Serum level of β-hCG.
3. Doppler blood flow velocity waveforms using Doppler indices (Systolic / diastolic (S/D) ratio, Resistance Index (RI) and Pulsatility Index (PI)).

The evacuation was done by the means of suction curettage and specimens were sent for histopathology.

All the cases were given low dose combined oral contraceptive pills ((Ethenylestradiol 0.03mg, Levonorgestrel 0.15mg) Microgynon ED® and ferrous fumarate) after evacuation of the molar pregnancy.

In the follow-up examination after evacuation of the uterus (in 1, 2 ,4 and 6 weeks after evacuation) all the patients were examined clinically, serum level of β-hCG measurement done in Radio Active Isotope Clinical Laboratory and Doppler examination using ultrasound duplex system using transvaginal probe 5-7.5 MHz frequency.

This Duplex System combines B-mode imaging (linear and sector probes) and bidirectional pulsed coloured Doppler technique with real time spectral analysis.

Uterine artery examination (both on the right and left sides) was done using 5MHz transvaginal probe with pulsed and colour Doppler facilities by the same radiologist. Colour Doppler was used to identify vessels of interest and serves as guide for pulsed Doppler velocimetry studies.

The patients were examined in dorsal position with four principle movement of the probe:

1. Sliding: Insertion into the vagina downward and backward.
2. Rocking: Upward and downward movement in the anteroposterior plane.
3. Panning: Horizontal movement from left to right.
4. Rotating: Circular movement of 90 degrees from longitudinal to transverse view.

Statistical Analysis

Analysis consisted of ***Student t-test. Correlation Coefficient*** from ***linear regression analysis*** was also applied.

P-value of < 0.05 was considered statistically significant.

P-value of < 0.01 was considered statistically highly significant.

Correlation coefficient (r) value < 0.5 indicates weak correlation.

Correlation coefficient (r) value > 0.5 indicates moderate correlation.

Correlation coefficient (r) value > 0.7 indicates strong correlation.

(r) value could be (+ve) indicating direct correlation.

(r) value could be (-ve) indicating inverse correlation.

Results

Table 1 show the clinical characteristics of the patients regarding their age, gravidity, parity and number of abortion.

	Mean±SD (Min-Max)
AGE	23.48±6.62 (15-35)
PARA	2.96±1.97 (1-7)
GRAVIDA	1.28±1.62 (0-5)
ABORTION	0.68±0.80 (0-3)

Table 2 Show the Color Doppler indices(S/D ratio, PI, RI) and β-hCG level before and after evacuation of vesicular mole.

	S/D	PI	RI	β-hCG
PRE	2.41±1.33 (1.02-7.70)	1.03±0.52 (0.31-3.20)	0.49±0.10 (0.30-0.80)	1743.72±1036.87 (208-5000)
1 WEEK	3.16±1.31 (1.90-8.01)	1.45±0.49 (0.70-3.30)	0.60±0.10 (0.40-0.78)	675.32±490.49 (20-2500)
2 WEKS	5.24±2.08 (2.60-13.20)	2.08±1.67 (1.05-9.80)	0.70±0.11 (0.50-0.93)	480.96±560.31 (7-3000)
4 WEEKS	7.43±1.99 (1.46-9.70)	2.52±0.70 (1.08-3.70)	0.81±0.09 (0.59-0.99)	416.28±901.98 (19-4700)
6 WEEKS	9.32±2.40 (1.50-11.20)	3.74±1.41 (1.01-5.60)	0.92±0.13 (0.59-1.10)	367.40±1189.88 (5-6000)
P value				
Pre X1 w	0.0001*	0.0001*	0.0001*	0.0001*
Pre X2 w	0.0001*	0.005*	0.0001*	0.0001*
Pre X4 w	0.0001*	0.0001*	0.0001*	0.0001*
Pre X6 w	0.0001*	0.0001*	0.0001*	0.0001*
1 w X2 w	0.0001*	0.088	0.0001*	0.0001*
1 w X4 w	0.0001*	0.0001*	0.0001*	0.038*
1 w X6 w	0.0001*	0.0001*	0.0001*	0.099
2 w X4 w	0.0001*	0.196	0.0001*	0.439
2 w X6 w	0.0001*	0.001*	0.0001*	0.438
4 w X6 w	0.0001*	0.0001*	0.0001*	0.453

*Significant difference using paired t-test.

The Systolic-Diastolic (S/D) ratio in the Uterine Arteries before and after evacuation of Vesicular Mole

It can be observed that S/D ratio in the right uterine artery was continuously increasing during follow-up visits, S/D ratio in the right uterine artery (2.4 ± 1.33) before evacuation of the uterus. It was increased to (3.16 ± 1.31) in the first week after evacuation (P=0.0001) and to (5.24 ± 2.08) in the second week after evacuation (P=0.0001). It continued to rise to (7.43 ± 1.99) in the fourth week after evacuation (P=0.0001) until it reaches a value of (9.32 ± 2.40) in the sixth week post-evacuation (P= 0.0001). ***(Figure 1)***

In the left uterine artery the S/D ratio showed also continuous increase similar to that of the right uterine artery indicating an increase of the vascular resistance after evacuation of the uterus.

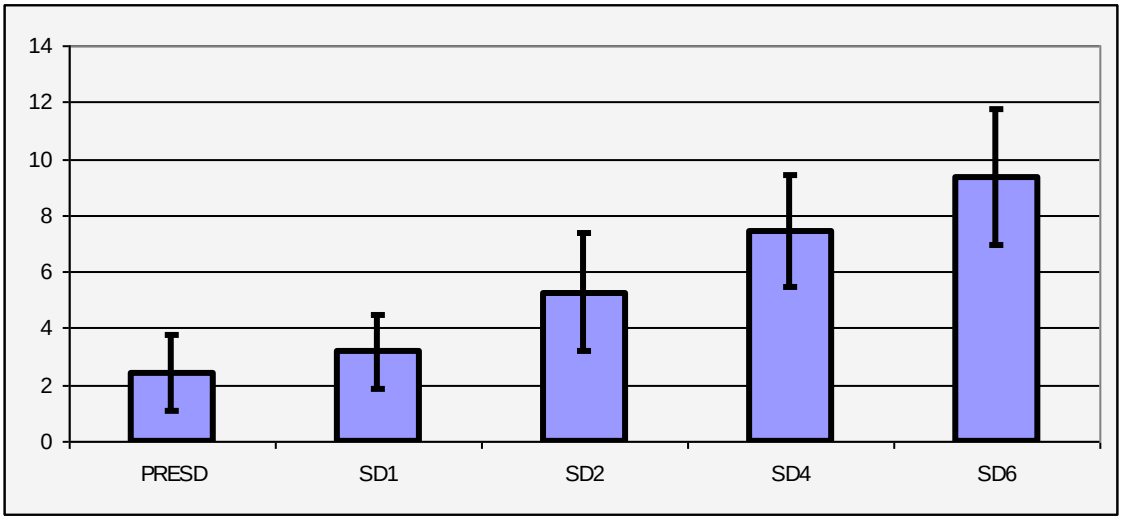

Figure 1. *The S/D ratio in the uterine artery before and after evacuation of vesicular mole.*

The Pulsatility Index (PI) in the Uterine Arteries before and after evacuation of Vesicular Mole

The Pulsatility Index (PI) in both right and left uterine arteries was continuously increasing during follow-up visits. In the right uterine artery PI was (1.03±0.52) before evacuation of the uterus. After evacuation it increases to (1.45±0.49) in the first week after evacuation (P=0.0001), to (2.08±1.67) in the second week after evacuation (P=0.005), to (2.52±0.70) in the fourth week after evacuation (P=0.0001).This increase continued until it reached (3.74±1.41) in the sixth week after evacuation (P=0.0001).

In the left uterine artery, the PI index showed also continuous increase similar to that in the right uterine artery indicating an increase of the vascular resistance after evacuation of the uterus. ***(Figure 2)***

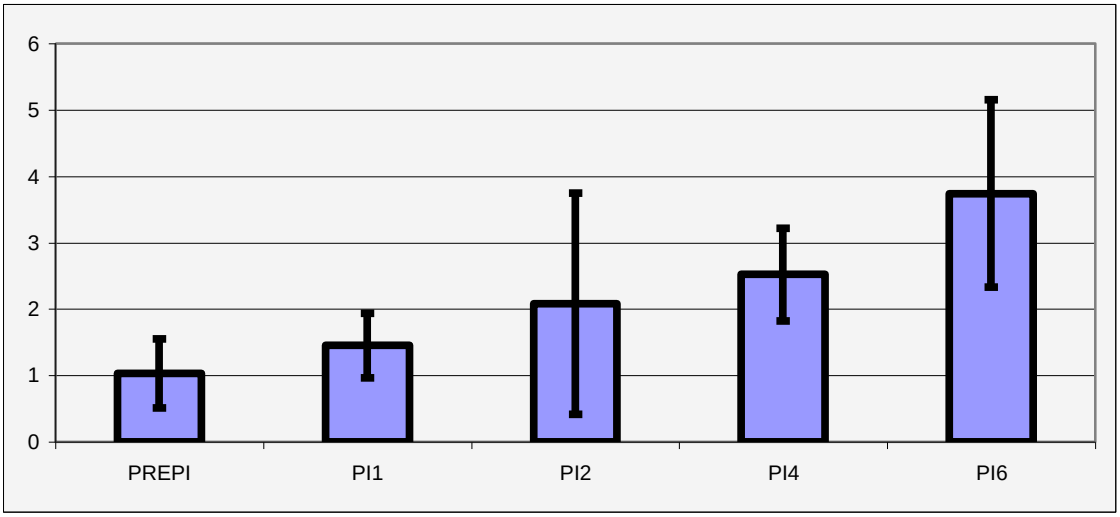

Figure 2.*The PI in the uterine artery before and after evacuation of vesicular mole*

The Resistance Index (RI) in the Uterine Arteries before and after evacuation of Vesicular Mole

It can be observed that the resistance index (RI) in both right and left uterine arteries was continuously increasing during the follow-up visits. In the right uterine artery RI was (0.49±0.10) before evacuation of the uterus. It increased to (0.60±0.10) in the first week after evacuation (P=0.0001) and to (0.70±0.11) in the second week after evacuation (P=0.0001), this increase continues until it reached (0.92±0.13) in the sixth week after evacuation (P=0.0001). ***(Figure 3)*** In the left uterine artery, the RI index showed also continuous increase similar to that in the right uterine artery indicating an increase of the vascular resistance after evacuation of the uterus.

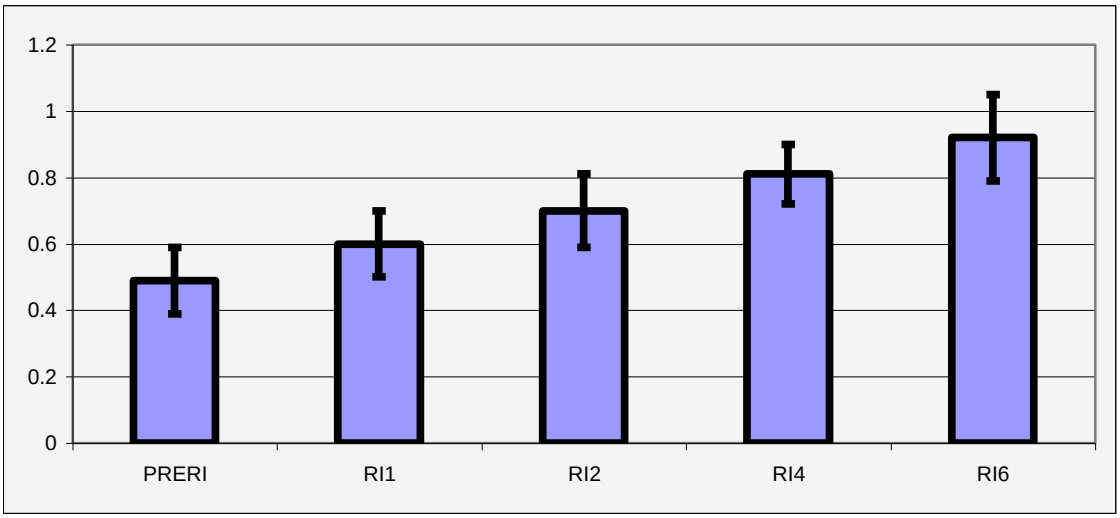

Figure 3.*The RI in the uterine artery before and after evacuation of vesicular mole.*

The β-hCG level before and after evacuation of Vesicular Mole

Before evacuation of the uterus β-hCG level was (1743.72±1036.87)IU/ml. It decreased to (675.32±490.49) IU/ml in the first week after evacuation (P=0.0001) and to (480±560.31) IU/ml in the second week after evacuation of the uterus (P=0.0001) and to (416.28±901.98)IU/ml in the fourth week after evacuation of the uterus (P=0.0001) and continues to decrease until it reached (367±1189.88) IU/ml in the sixth week after evacuation of the uterus (P=0.0001). ***(Figure 4)***

It can be observed that in twenty-two out of these twenty-five cases β-hCG level was continuously decreasing during the follow-up visits. These twenty-two achieved spontaneous resolution with gradual decrements in their β-hCG level after six weeks of evacuation of the uterus until they reach the normal level.

In the reminder three cases:

- In two cases β-hCG level was gradually decreasing but did not reach the normal level for which Dilatation & Curettage (D&C) was done. It revealed persistent trophoblastic tissue and received prophylactic chemotherapy.
- One case did not show significant decrement in β-hCG level in the first week after evacuation of the uterus, then β-hCG level show consistent increase in the sixth week after evacuation of the uterus with persistent vaginal bleeding for which D&C biopsy proved to be choriocarcinoma. And total abdominal hysterectomy was done for this patient after failure to respond to chemotherapy.

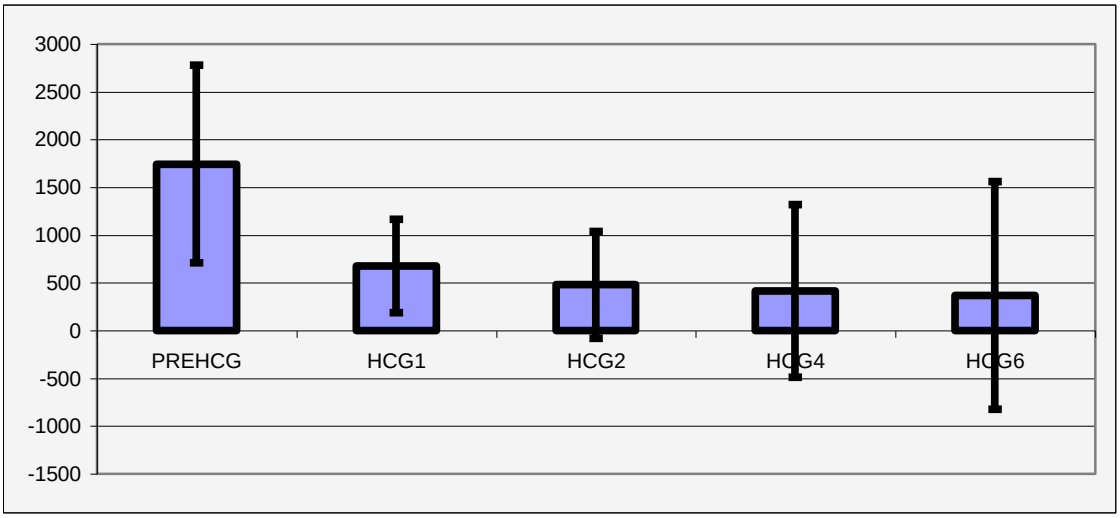

Figure 4.*The concentration of β-hCG before and after evacuation of vesicular mole.*

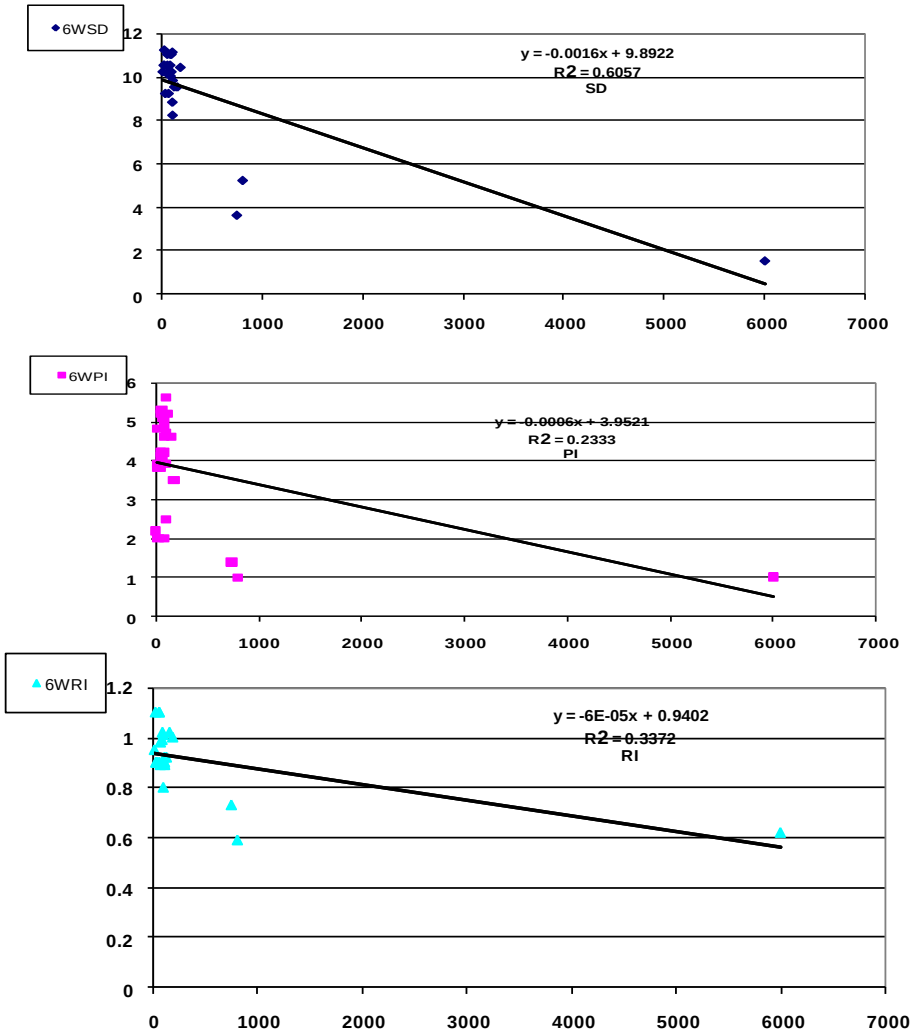

Figure 5

There is strong correlation between the fall in serum level of β-hCG and the rise of Doppler indices throughout the course of follow-up. This relationship is demonstrated in ***Figure 5.***

There is significant strong correlation between the fall in β-hCG level and the rise in S/D ratio (r) = - o.778 (strong inverse correlation). (P=0.0001) The

value of (r) between β-hCG and PI = - 0.483 (weak inverse correlation).

The (r) value between β-hCG and RI = - 0.581. (P=0.002). There is moderate inverse correlation which is significant.

Discussion

Gestational trophoblastic disease exhibit hyperdynamic flow in the uterine circulation, i.e. high peak systolic velocity and low resistance (RI) values, which is not displayed in normal non-pregnant uterus. This may reflect the inherent characteristics of trophoblasts in destroying the uterine vasculature. The uterine artery consequently exhibit high velocity and low impedance because of the low resistance downstream circulation. This is an important indicator of the presence of trophoblatic activity in this abnormal gestation.

After evacuation of the uterus, it can be observed that S/D ratio, PI, RI in both the right and left uterine arteries was continuously increasing during the follow-up visits, indicating an increase of the vascular resistance of the uterus.

In the Two cases with persistent trophoblastic disease there was plateauing of the values and no continuous increase of the resistance indices but a decrease in all indices in the case which developed choriocarcinoma. There was an increase in all Doppler indices following evacuation of the uteri in patients having uneventful course of pregnancy. [13]

Abd El Aal & Kunzel demonstrated that there is a sharp decrease in uterine blood flow velocity following uneventful abortion. [14] Similar results were obtained by Dillon et al. They demonstrated that the peak systolic velocity and end-diastolic flow velocity of the uterine arteries returned to normal after clinical remission of trophoblastic disease was achieved indicating that there was no more trophoblastic mass.[15]

Jauniaux et al demonstrated that the peak systolic velocity of the uterine arteries begin to rise at 5-8 weeks of normal gestation, which indicates increased blood flow to meet the demands of the developing conceptus. A decrease in the RI values of the uterine arteries followed at 9-12 weeks gestation, implying trophoblastic destruction of the uterine vasculature to establish low impedance uteroplacental circulation. They believed that Color Doppler Ultrasonography will improve our understanding of the pathophysiology of various pregnancy disorders that alert the placental circulation and that color Doppler ultrasonography is useful for the prenatal differential diagnosis of intrauterine masses. [16]

The uterine hemodynamic changes in gestational trophoblastic disease are someway similar to that of uteroplacental hemodynamics at emberyogenesis.

Serial measurements of serum β-hCG level is a method widely used to monitor the behavior of residual trophoblastic tissue after evacuation of hydatidiform mole. These so called post-evacuation regression curves allow early identification of patients with persistent trophoblastic disease.

Reported meantime intervals required for normalization of serum hCG in patients with spontaneous regression range from 49 to 99 days with maximal disappearance times between 98 and 278 days. [9]

It has been observed in this study that in 22 out of 25 cases of this study β-hCG level was continuously decreasing during follow-up visits. In one case β-hCG level did not show significant decrease in the follow-up visits with sharp increase in the sixth week post-evacuation of its β-hCG level with decline of all Doppler indices for which D&C biopsy done and revealed choriocarcinoma.

In the remaining two cases the Doppler indices showed plateauing values and the serum level of β-hCG was gradually declining but not reached normal level for which D&C showed persistent gestational trophoblastic disease.

Kohorn et al reported that weekly serial levels of serum hCG remain the most accurate, reliable and definitive arbiter of treatment management of gestational trophoblastic disease. [17]

Rob et al reported that spontaneous regression in β-hCG level in serum is more rapid in patients with partial mole, slower in complete mole and invasive mole. [18]

In this study one patient out of 25 cases of hydatidiform mole was partial mole as evidenced by ultrasound presence of fetal parts and it had a relatively more rapid spontaneous regression of serum β-hCG level after evacuation as compared to the reminder cases of complete hydatidiform mole.

Cameron et al reported that serial serum β-hCG concentration after evacuation would require approximately 4-12 weeks for spontaneous regression of uncomplicated hydatidiform mole. Therefore, the diagnosis of persistent gestational trophoblastic disease is rather an arbitrary decision based on a sustained level of serum β-hCG for a certain period. [19]

Maymon et al found that in the post-evacuation visits of patients with vesicular mole, those who

developed persistent gestational trophoblastic disease where their serum β-hCG levels were not different from some of other patients who showed spontaneous regression. However, their S/D & PI values remained low. They found that the regression of disease could be reliably assessed by observing the changes in the low resistance flow which parallel the gradual decrements in β-hCG levels. [20]

Similar observation have been made by Carter et al [21], Kawano et al [22] and Chan et al [23] who demonstrated that the decrease in vascularity and the increase in PI of uterine arteries were closely related with the decrease in the serum β-hCG levels.

Tapper et al [24] concluded that the response of gestational trophoblastic neoplasia to chemotherapy could be reliably assessed by observing changes in the flow resistance which parallel the gradual decrements in serial measurement of β-hCG levels. This could be confirmed by the present observations in this study.

Yong-Won et al [25] concluded that vascular changes displayed on Color Doppler Scanning might, thus, complement the application of β-hCG levels in post-molar pregnancy surveillance. This can be supported by the findings in this study.

Conclusion

Color Doppler flow is non-invasive, reproducible, useful and reliable diagnostic approach for the diagnosis and management of patients suffering from gestational trophoblastic disease in conjunction with serial serum β-hCG monitoring.

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* Professor and Consultant in Obstetrics & Gynaecology
Department of Obstetrics & Gynaecology
College of Medicine, AL-Mustansirya University, AL-Yarmouk Teaching Hospital

** Senior Obstetrician & Gynaecologist
Department of Obstetrics & Gynaecology , AL-Yarmouk Teaching Hospital

*** Consultant Obstetrician & Gynaecologist
Department of Obstetrics & Gynaecology, AL-Yarmouk Teaching Hospital

**** Senior Lecturer , National Diabetes Center, AL-Mustansirya University