ß hCG AND UTERINE DOPPLER VELOCIMETRY STUDIES IN POSTMOLAR SURVEILLANCE

R. RAJAN ● ROSHINI JOHN

SUMMARY

We have developed standard norms and patterns of ß hCG and Doppler Index (SD ratio) curves : (i) for excluding the possibility of postmolar trophoblastic disease (PMTD) (ii) for early detection of PMTD; and (iii) for evaluation of therapeutic response of PMTD. These standard curves could be employed for plotting the patient's values for prognosticating the postmolar events. This study advances evidences to support the use of Doppler study as an acceptable and practical alternative to ß hCG surveillance. We also prove that early detection, which is possible by ß hCH or Doppler surveillance, leads to complete cure of PMTD with single agent chemotherapy (methotrexate) over an average of 3 treatment courses.

INTRODUCTION

The purpose of this study is to develop standard norms and patterns of ß hCG regression curves (i) in patients taking a benign course after termination of molar gestation; (ii) in those who develop postmolar trophoblastic disease (PMTD); and (iii) in whom the trophoblastic disease is successfully treated. These standard curves could be used among patients who had recent molar evacuations for plotting the patient's values to enable early diagnosis or exclusion of postmolar trophoblastic disease.

We have also employed uterine blood flow studies, employing duplex Doppler system, in the surveillance of postmolar disease and in prognosticating the therapeutic response in trophoblastic disease. Based on this study standard Doppler velocimetry patterns for the three categories of patients have been developed. These Doppler patterns developed by us are

Dept. of OBS & Gyn., Medical College Hosp. Kerala.
Accepted for Publication on 31.1.1995

compared with our standard ß hCG regression curves, in order to identify if monitoring by serial Doppler studies could be an effective and simpler alternate of ß hCG surveillance.

MATERIALS AND METHODS

The protocol employed for early detection or exclusion of postmolar trophoblastic disease in patients who had recent evacuation of vesicular more included: (i) serial ß hCG quantification; (ii) B mode ultrasound study of the myometrium and endometrial cavity; (iii) Doppler velocimetry of uterine blood flow and (iv) B mode ultrasound evaluation of ovaries. In addition chest X-ray and if mandated sonographic evaluation of liver had been also considered. The surveillance study was initiated as early as he first week of termination of molar gestation.

ß hCG quantification : Serum ß hCG study was complemented by urinary ELISA tests for quantification of the gonadotropin titer. At the time of surgical termination of molar gestation the first serum sample was collected, and this was followed by serial serum study at 7 to 10 days interval. If the titer showed precipitous decline the follow-up studies were on urine tests. Gravindex (sensitivity, 1300 - 1700 mIU), ß Gravindex (250 - 500 mIU), Pregcolor (100 mIU) and Icon II (25-50 mIU) were employed in the descending order and a fairly accurate semiquantification of ß hCG titer regression could be deduced by these simple urine test (Rajan, 1992). Alternately, the equally sensitive method is to perform urinary ELISA test (Icon II) in dilution in various gradations. Negative urine test (Icon II) indicates that the ß hCG titer is <25 mIU. This last negative finding is preferably confirmed by a quantitative serum study, and ß hCG regression is considered complete if the titer had gone down to <15 mIU/ml.

Concurrent with the decline in ß hCG titer, the patient establishers regular ovulatory menstrual cycle. Vaginal ultrasound studies are frequently employed to determine the ovulatory status. We believe that a series of regular ovulations positively denote complete regression of hCG and hence of proof for complete cure of the disease. By and large, regular ovulatory menstrual cycles complemented by a series of negative urinary ELISA tests preclude the development of PMTD. Six consecutive ovulatory cycles, with consistently negative urine test, have been considered the cut-off for attempting next conception.

If the ß hCG regression is perfect and the patient establishes regular ovulatory menstrual cycles none of the investigations mentioned below are indicated. However, on the contrary, abnormal regression of ß hCG titer is the earliest evidence of postmolar trophoblastic disease (PMTD), and certainly mandates as immediate sonographic evaluation of the uterus.

Transvaginal sonography (TVS) of the uterus: Endometrial cavity is surveyed for evidence of incomplete evacuation of moles. The Myometrium is inspected carefully for evidence of discrete myometrial nodules (invasive mole) or diffuse vascular shadows (choriocarcinoma). The sonographic diagnostic clue is that if the uterine cavity line could be clearly imaged, and 'speckled appearance' (sonographic appearance of vesicular mole) or complex nodule is located in the myometrium the diagnosis is invasive

mole. On the contrary if the uterine cavity line is not demarcated the 'speckled appearance' with evidence of blood clot will indicate incomplete evacuation. In effect TVS enables identifying and differentiating the following 4 presentations of the trophoblastic diseases in subjects with abnormal ß hCG regression: (i) incomplete molar evacuation; (ii) invasive mole; (iii) choriocarcinoma and (iv) clinical choriocarcinoma (Rajan and Rajan, 1991). Incidentally an intrauterine pregnancy as a cause of elevated ß hCG titer also should be considered at ultrasound evaluation.

Incomplete molar evacuation is managed by surgical emptying of the uterus. Myometrial nodules (invasive mole) are managed by methotrexate therapy or combination of methotrexate and surgical enucleation of the nodule. Myometrial diffuse vascular shadow (choriocarcinoma) is treated by methotrexate. If no pathology is detected in the uterus the abnormal titer is attributed to 'clinical choriocarcinoma', and treated with methotrexate. However, one should look for vaginal, pulmonary or hepatic nodules for any clue in such patients. After initiating the optimal treatment, regression of the myometrial pathology is monitored at serial sonographic studies at 1 to 2 weeks interval. In addition ß hCG and Doppler Velocimetry surveillance are continued to the state of complete cure of the disease.

Doppler velocimetry studies : Abdominal Doppler employing 3 MHz probe (continuous Wave Form) has been used in the current study, to evaluate the blood flow velocity in the arcuate artery and on the vascular shadows inside the uterus. Molar gestations and PMTD are found to evidence low resistance, high flow velocity pattern in the uterine artery with increased diastolic filling and reduced pulsatility (Kurjak, et al., 1992). The SD ratio (systolic-diastolic ratio) has been calculated, and was found to be low in these subjects, in the range of 2.5 for molar gestations and 1.5 for PMTD. Once treatment is initiated, serial monitoring of the SD ratio at 7 to 10 days interval enabled determination of declining vascularity of the uterus (increase in SD ratio), thereby proving resolution of the disease process. With complete cure of the trophoblastic disease, the uterine blood flow reverts to a high resistance, decreased flow velocity pattern as reflected by the SD ratio of 4.7 - 5 or quite often an 'absent and diastolic velocity' (AEDV).

The Doppler velocimetry study has been found equally prompt and promising as ß hCG quantification in early diagnosis and monitoring of PMTD. In fact, the endocrine study and the vascular study are reflecting one and the same phenomenon in a different format, so much so, it appears that one the two tests will be quite sufficient for postmolar surveillance (Rajan and Roshini, 1994).

Lutein cysts: Sonographic evaluation of ovaries for evidence of lutein cysts is part of postmolar surveillance. Whenever ultrasound studies are conducted the adnexal structures are also imaged and the ovarian enlargement, if present are noted and measured. However, lutein cysts regress very slowly, so much so, we do not attribute any prognostic value for this finding.

RESULTS

This study is related to 55 patients investigated and treated over a period of 2 yrs and 8 months, between April, 1992

and November, 1994: They include 31 subjects diagnosed to have vesicular mole and another 24 subjects recruited for postmolar surveillance between 1 week to 7 months after termination of molar gestation.

There were 21 subjects who had normal regression of hCG titer, and these patients did not develop PMTD, and many of them could be followed for regular menstrual cycles and some had conceived a second pregnancy later. Based on the hCG pattern of these patients we have developed a normal ß hCG regression curve (fig. I and Table I). As per this data, the average hCG value immediately after molar evacuation was 60,000 mIU/ml, which declined to nearly 20,000 mIU/ml over a period of one week. The decline was quite precipitous from this point, and by the 2nd week the titer was 1,000 mIU/ml, which declined to 100mIU/lm in the 3rd week and to the range of 25-30 mIU/ml by the 4th week. Complete regression has been achieved by 5 to 6 weeks from the time of evacuation.

A correspondings slope of increased uterine vascular resistance (high SD ratio) was observed in these normal subjects at Doppler surveillance (Fig. II, Table I). The usual SD ratio for molar gestation was 2.5, which increased to 2.7 by one week following evacuation, and to 3.8 by 2nd week and 4.7 by the 3rd week. By the 4th week of molar evacuation and beyond, the uterine flow evidenced considerable vascular resistance with diastolic notch and almost reached the stage of AEDV.

Similarly of ß hCG pattern and Doppler velocimetry studies were evaluated in subjects who had PMTD. Among the 17 subjects of PMTD in whom the ß hCG pattern could be followed, the titer was ranging from 40,000 to 50,000 mIU/lm in the immediate post-evacuation period, 20,000 mIU/ml at

Table I
ß hCG and Uterine Doppler in Postmolar subjects having a benign course

Weeks following evacuation	ß hCG MIU/ml	SD Ratio
0	60,000	2.5
1	20,000	2.7
2	1,000	3.8
3	100	4.7
4	25 - 50	5.0 AEDV
5	<2	
6	<25	

AEDV : absent end diastolic velocity

Table II
ß hCG and Doppler study in successfully treated postmolar disease

Methotrexate course	ß hCG MIU/ml	SD Ratio
Pretreatment	40,000 - 50,000	1.5
After 1st course	6,000	2.2
After 2nd course	500 - 1000	3.0
After 3rd course	<100	4 - 4.5
After 4 weeks of initiation	<25	NOTCH/AEDV

one week, and remained in the range of 10,000 to 20,000 mIU/ml in the subsequent 2 weeks (Fig. III). However, in normal subjects with a benign course the titer would have declined to 1000 mIU/ml by 2 weeks, and remained less than 50 mIU/ml by 3rd and 4th week. Thus ß hCG surveillance from the 1st week of termination of molar gestation optimizes the earliest detection of PMTD. Uterine Doppler studies record and average SD ratio of 1.5 for subjects with PMTD, whereas those having a benign course record a SD ratio of 3.8 to 4.7 or an absent diastolic flow.

Patients who have been successfully treated with methotrexate (0.4 mg/kg/day), in a total dose of 50 to 75 mg/course and similar 2 or 3 courses, showed the following ß hCG (15 patients studied) and Doppler (9 patients studied) patterns. From the pretreatment titer of 40,000 to 50,000 mIU/ml, ß hCG declined to 6,000 by the first treatment course, and to 500 to 1000 mIU/ml after 2nd course of methotrexate, and to less than 100 mIU/ml usually by the third course. Almost the regression was complete by 4 weeks of initiation of treatment (Fig. IV and Table II). Few of these patients underwent enucleation of myometrial nodule in addition to prior chemotherapy.

Equally attractive information could be gathered from the serial Doppler study in 9 successfully treated patients : From the pretreatment range of 1.5 the SD ratio increased to 2.2 by the first treatment course, then to 3 by second methotrexate schedule and to 4.0 to 4.5 by the completion of 3rd course. By 4 weeks of initiation of methotrexate therapy the uterine flow velocity evidenced significant vascular resistance with diastolic notching and almost AEDV (Fig. V and Table II).

One patient with a postmolar disease (myometrial nodule) who was diagnosed by the 4th week of molar evacuation and recruited for methotrexate therapy is described in Fig. VI. She had a pretreatment ß hCG titer of 20,000 and SD ratio 1.5, and the myometrial nodule was 3 cms in diameter. By the completion of three course of methotrexate, she regressed the hCG titer

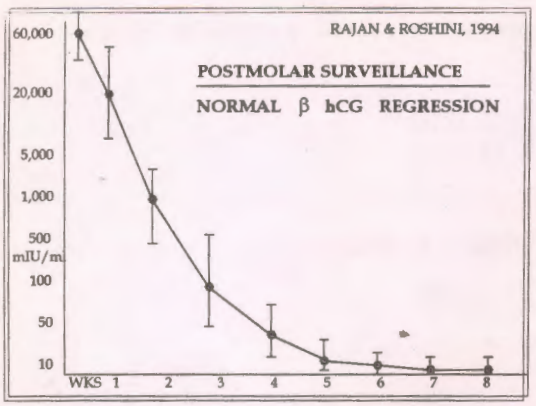

Fig. 1

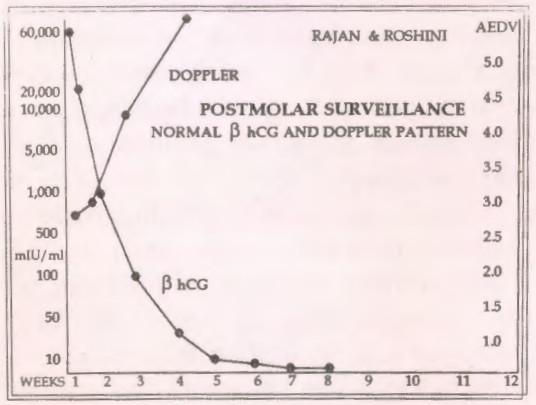

Fig. 2

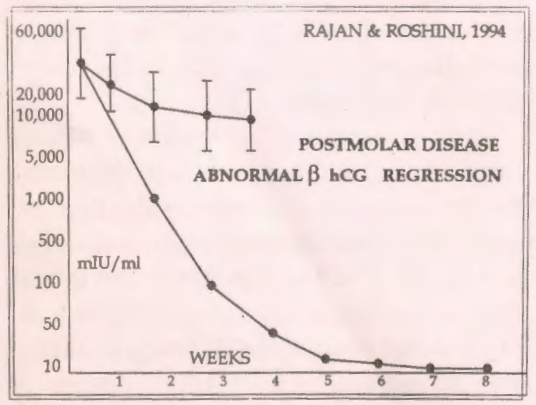

Fig. 3

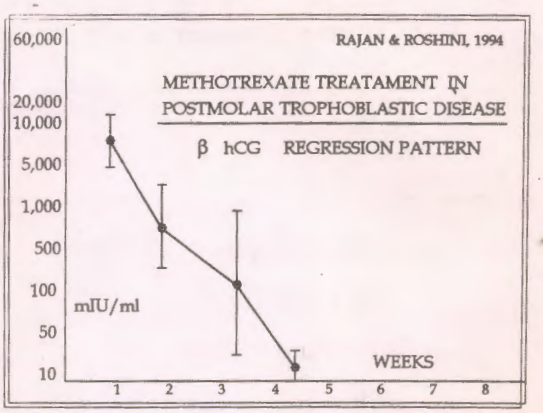

Fig. 4

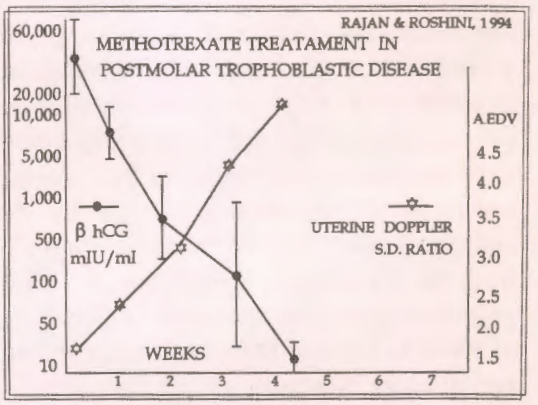

Fig. 5

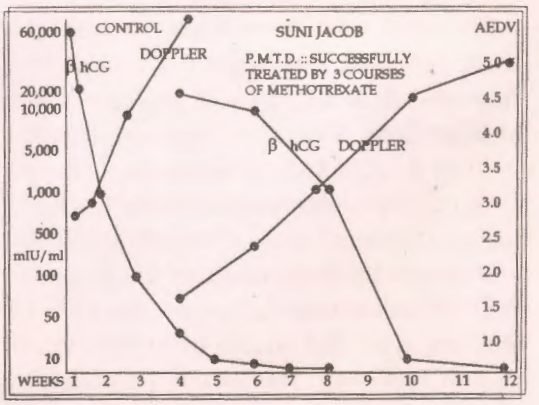

Fig. 6

to 5mIU, and increased the SD ratio to 5.0, with complete disappearance of the nodule.

Among the 17 subjects with PMTD early treatment within 4 weeks of evacuation was initiated in 15 patients, and all them were completely cured with restoration of their fertility. Those who desired fertility could achieve a conception. However, the two subjects in whom the treatment was initiated after 8 and 14 weeks the disease could not be cured by methotrexate alone, had to resort to hysterectomy.

DISCUSSION

This study fanning over a period of 2 years and 8 months, involving 55 patients presenting with trophoblastic disease (vesicular mole or PMTD), was utilized to develop the following standards of ß hCG regression and uterine Doppler velocimetry pattern. These standard norms could be employed for plotting patient particulars for early diagnosis of PMTD and evaluation of treatment response in trophoblastic disease.

1. By studying the ß hCG regression pattern in 21 postmolar subjects with a benign course, a standard normal ß hCG regression curve has been developed (Fig. 1). This regression curve is similar to that developed by Morrow in 1984. If the patient's regression pattern is in accordance to his standard curve there is no fear of development PMTD.

2. Similarly, a standard normal pattern of Dopple index (SD ratio) has been evolved which runs parallel to the normal ß hCG regression curve (Fig. II). We argue that serial uterine Doppler velocimetry study will emerge as an equally effective alternate to ß hCG surveillance in screening postmolar subjects.

3. We have also worked out a standard pattern of ß hCG regression in PMTD by studying 17 patients. This curve, plotted from the 1st week of molar evacuation, should help one discriminating the benign from the malignant course with 2 to 3 weeks of termination of molar gestation. We feel this approach offers for the earliest diagnosis of PMTD.

4. A corresponding uterine Doppler study indicates low resistance-high flow velocity (SD ratio : 1.5) in subjects developing PMTD. Thus Doppler study emerges as a viable alternative for the early detection of PMTD.

5. The fact that all the 15 subjects were cured of PMTD, in whom the treatment was offered within 2 to 4 weeks of molar evacuation, stress the importance of early diagnosis. We hold that early diagnosis and decision making are possible by employing either serial ß hCG or Doppler velocimetry studies.

6 Just as screening for PMTD. we prove that evaluation of therapeutic response in PMTD is also equally and efficiently handled by either of the two investigations. In Fig. IV and V the normal regression pattern of ß hCG and SD ratio slope in the successfully treated patients are plotted. By plotting the patient's values against these curves, early recognition of therapeutic response is feasible. If the patient's values do not correspond to the standard pattern one can decide on alternate therapeutic approach without much delay.

7. Weekly B mode and Doppler mode studies have emerged as a simpler and equally effective alternate to ß hCG surveillance, both in postmolar evaluation and treatment

of PMTD. High uterine SD ratio to the stage of AEDV complemented by regular ovulatory menstrual cycles could be considered the ultimate in negating the risk of trophoblastic disease.

REFERENCES

1. *Kurjak, A, Zalud, I, and Dukic, V.: An Atlas of Ultrasonography in Obstetrics and Gynecology, Ed. Kurjak, A. : The Partehnon Publishing Group, New Jersey, U.S.A., 1992, p. 201.*
2. *Morrow, C.P. : Clin. Obstet Gynec. 27 : 213, 1984.*
3. *Rajan, R. and Rajan, V. : Endovaginal Sonography in Infertility, Gynecology and Obstetrics. : 1st Edn. 1991, p 1.*
4. *Rajan, R. : Postgraduate Reproductive Endocrinology. : 3rd Edn. 1992, p. 514*
5. *Rajan, R., and Roshini, J. : Gynecological Oncology, by IAHR and MKOGS. lecture: β hCG and Doppler in Postmolar Surveillance. 1st and 2nd October, 1994, Cochin.*