Hydatidiform Mole and Post-evacuation Regression Patterns of Serum Beta Human Chorionic Gonadotrophin

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Summary

Eighty-nine patients who had hydatidiform moles evacuated at the General Hospital, Kuala Lumpur, were followed with serum βhCG determinations from October 1988 to June 1991. A regression curve for serum βhCG, as measured by RIA, was derived from the results of 47 of the patients who demonstrated spontaneous regression of serum βhCG titres. All 47 patients had normal serum titres at 135 days after evacuation. The mean time taken to reach normal level was 82.6 days, while the range was 39 to 135 days (5 to 19 weeks).

Key words: Hydatidiform mole, hCG, βhCG, regression.

Introduction

Human chorionic gonadotrophin (hCG) is a glycoprotein hormone which consists of 2 dissimilar subunits, alpha and beta, that are joined noncovalently[1]. The hormone is produced by normal and neoplastic trophoblastic tissue. It has been observed that in patients with hydatidiform mole the circulating serum levels of intact hCG and free beta subunit of human chorionic gonadotrophin (βhCG) are considerably increased, while the levels of free a-subunit hCG are normal or slightly increased when compared with women with normal pregnancies[2].

The rate of serum βhCG regression in patients following the evacuation of hydatidiform moles (HM) has been reported, by several workers to follow a log-exponential decline[3,4,5,6]. The serum βhCG concentration is recognised as an important prognostic indicator of gestational trophoblastic disease. However, reference values may not be extrapolated from one study to another because of population differences, and, in particular, because values are influenced by the analytical method and reference standard used. The objective of this study was to determine the rate of regression of serum βhCG in Malaysian women and to define limits which could be used to identify women with resistant disease or at risk of developing secondaries.

Patients and Methods

From October 1988 to June 1991, 89 patients who had histologically confirmed HM evacuated at the General Hospital, Kuala Lumpur, were referred to the Institute for Medical Research, Kuala Lumpur, for serum βhCG

determinations. Venous blood samples were collected after evacuation in the ward or before the second dilatation and curettage. Subsequent blood samples were collected at fortnightly intervals for 3 months and monthly for the next 3 months. This was followed by sample collection at 2 monthly intervals for 6 months and 4 monthly intervals for 1 year. Sera from the blood samples were stored at -20°C until assay. Quantitative serum βhCG levels were measured by radioimmunoassay (RIA) using Amerlex-M βhCG RIA kit. The kit uses an antiserum raised against the β-subunit of hCG. The assay has a sensitivity of 5.2 IU/L (first International Reference Preparation for hCG 75/537), while the precision of the assay at various βhCG concentrations is given in Table I. The within and between assay precisions ranged between 1.5% to 8.5% and 6.9% to 12.9% respectively. The serum βhCG value established as the normal level was <9 IU/L.

The βhCG results were analysed by the rankit method of linear transformation[7,8]. Correlation was determined by the least squares regression analysis.

Table I
Serum βhCG radioimmunoassay precision data

| βhCG dose (IU/L)	Coefficient of variation (%)	
	Within batch	Between batch
8.4	8.5	12.9
19.3	1.5	9.1
31.1	3.6	8.5
90.0	4.6	6.9
217.4	5.3	10.3

Results

During the study period, 52 patients demonstrated spontaneous regression of serum βhCG titres to normal levels. Nineteen patients defaulted follow-up before normalisation of serum βhCG levels, while 1 became pregnant during this period. Another 16 patients underwent treatment by chemotherapy, while 1 patient died.

Of the 52 patients who demonstrated spontaneous regression after evacuation, 5 patients' serum βhCG results were excluded from the analysis. Three patients were excluded because they either had a plateau of βhCG titres or persistent post-evacuation uterine bleeding. The other 2 patients' data were excluded because their βhCG regression curves had 3 or more values higher than the 95% confidence limits of the regression curve during the initial analysis. Fig 1 shows the individual regression curves of 4 patients whose serum hCG did not decline normally, superimposed upon the hCG regression envelope derived from the data of 47 patients.

Of the 47 patients in the study, 38 (80.8%) were Malays, 2 (4.3%) Chinese, 4 (8.5%) Indians and 3 (6.4%) Indonesians. The mean maternal age of the patients was 29.7 years and the range was 19 to 45 years. The mean gravidity was 4 and the range was 1 to 15 pregnancies.

The gestational age at the time of diagnosis, calculated from the date of the last menstrual period, gave a mean of 14.7 weeks while the range was 5 to 28 weeks. The calculated weekly mean titre values and the 95% confidence limits for the first 19 weeks after evacuation are shown in Fig 2. In some instances, when the values at 2 normal equivalent deviates (2 NED) below the mean were less than the detection limit, the latter was taken as the lower limit. The mean time taken by the patients' serum βhCG levels to decline to normal levels was 82.6 days after evacuation, while the range was 39 to 135 days (Table II). The mean number of βhCG titres determined before a normal level was attained was 5 (range 2 to 8). In Fig 3, the percentage cumulative cases
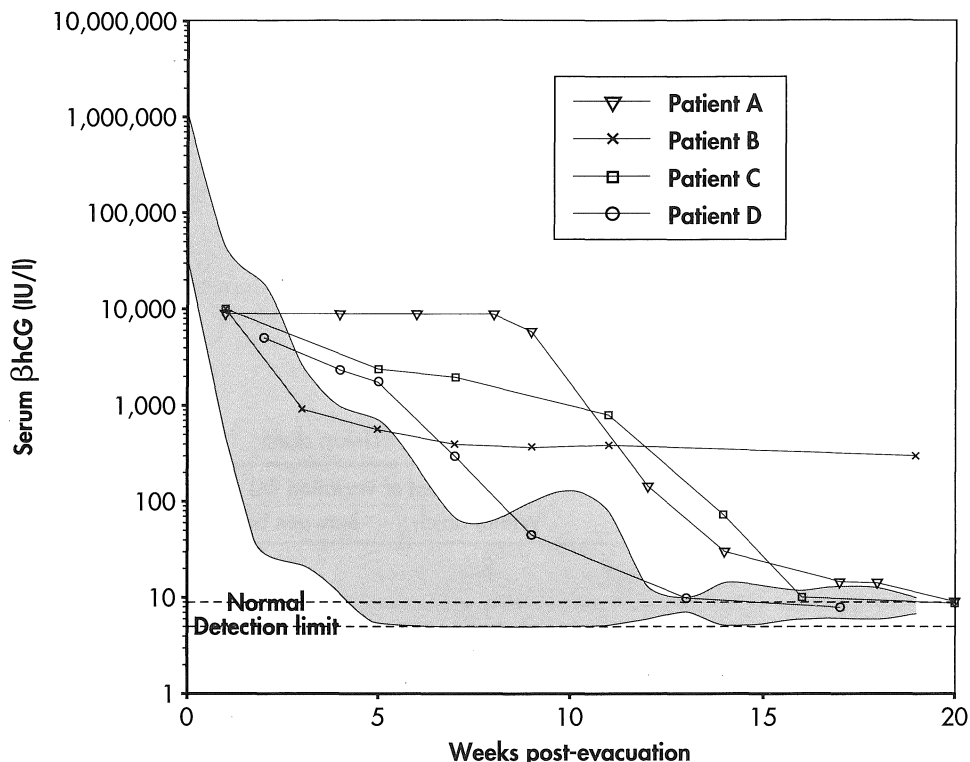
Fig 1: βhCG regression curves of 4 patients whose results were excluded from the reference envelope (stippled area). Patients A and B had plateaued βhCG titres which regressed over 20 and 33 weeks respectively while patients C and D had several raised values.

regressed versus time in weeks is presented. At 12 weeks after evacuation, 55% of the patients had achieved regression of serum βhCG titres while the majority (94%) had regressed by 18 weeks. The relationship of serum βhCG regression time with maternal age, gravidity, gestational age and the first available βhCG titre within 10 days post-evacuation was also analysed and found to be not significant (p>0.05).

Discussion

In our study, the time taken by the HM patients for their serum βhCG levels to regress to normal after evacuation ranged from 39 to 135 days. The mean time of 82.6 days is not very different from that reported by some others[4,5] (Table II). However, the maximum regression time is much less and comparable to that reported by Rotmensch et al[6]. Observed variations in regression time between different studies are in part due to method-related differences, such as the specificity and sensitivity of the assay used for βhCG determination, as well as biological differences between the population of subjects studied. It has been reported recently that there are at least 7 distinctly different molecules with hCG β-subunit immunoreactivity in the blood of individuals with pregnancy or trophoblast disease[9]. The different hCG/βhCG immunoassays used at different centres to monitor patients with HM and choriocarcinoma detect each of these 7 molecular forms to varying extents. Additionally, some centres may prolong the observation period in the absence of clinical disease or a marked elevation in hCG.
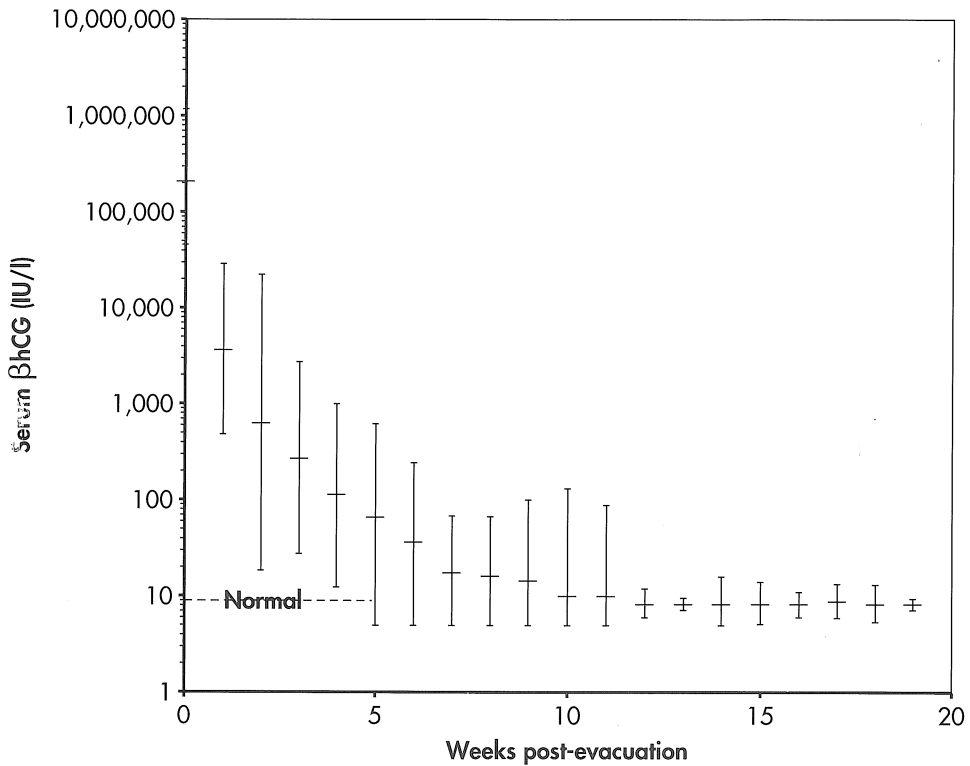
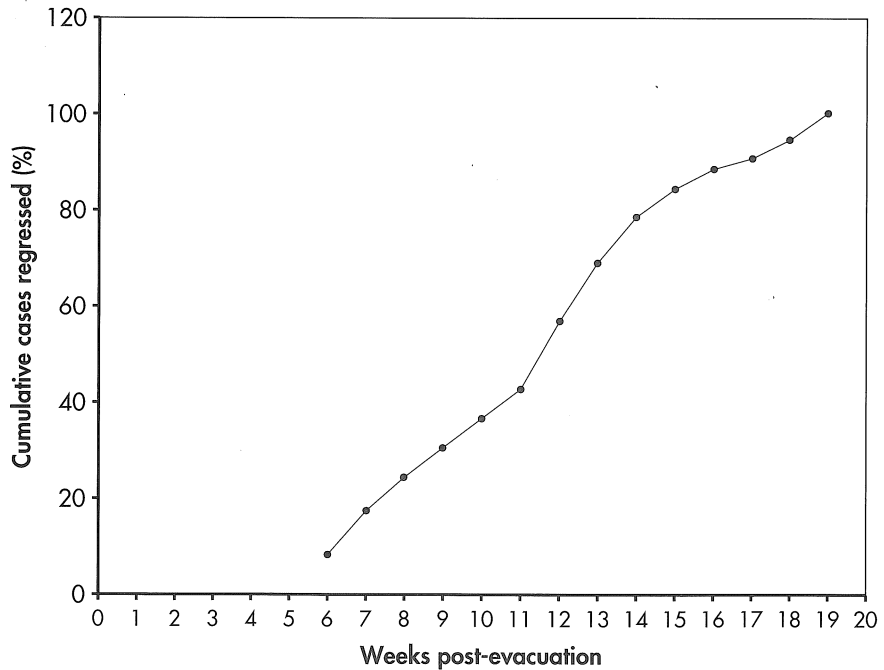Fig 2: The mean value and 95% confidence limits of the normal post-molar βhCG regression curve.

Fig 3: Cumulative frequency of cases of hydatidiform mole regressed versus time after evacuation.

Table II
Comparison of patients' serum βhCG regression data
following the evacuation of hydatidiform mole

Series	Year	No of patients	No of days to normal serum βhOG level		
			Mean	Median	Range
Ho Yuen et al[4]	1981	120	73.6	—	11-219
Franke et al[5]	1983	111	99.3	84	21-278
Rotmensch et al[6]	1986	63	—	49	7-105
This study	1991	47	82.6	85	39-135

It is clear, however, that serum hCG monitoring is extremely useful for identifying patients who are not regressing normally or who require treatment. Lurain and associates[10] support the use of individual patient hCG regression pattern, rather than deviations from a reference curve, in making treatment decisions. On the other hand, Schlaerth et al[11] treated 36% of their patients on the basis of deviations from a normal hCG regression curve. This compares with 18% of the patients in our study who received chemotherapy based on individual clinical and laboratory assessment.

Difficulties in the interpretation of hCG results, if luteinizing hormone cross-reactivity is excluded, arise especially in 2 situations. One, when the patients' results are mildly elevated, show fluctuations or are prolonged in returning to normal. Two, when a secondary rise in hCG occurs before or during remission and there is no immediate clinical evidence of a pregnancy or secondary disease. The first situation is illustrated by the data shown in Fig 1, where 2 patients with plateauing hCG regressed spontaneously over 20 weeks (A) and 33 weeks (B) respectively. A rather similar finding was reported by Schlaerth et al. Two of their patients who had abnormal regression curves but were temporarily lost to follow-up returned at 15 and 16 weeks respectively after evacuation in spontaneous remission. In contrast, 1 of their patients whose hCG titre plateaued at 600 IU/L 6 weeks after evacuation and then rose to 5,000 IU/L within 3 weeks had a cerebral haemorrhage and died before treatment was started. This highlights the need for early treatment intervention and also the dilemma of decision-making posed by the observation that there are patients with plateauing hCG titres who are capable of regressing spontaneously given sufficient time. While clinical assessment is important, signs and symptoms are not always present and reference to a hCG regression envelope, which defines the temporal changes in hCG concentration as reported in this study, can be invaluable for risk assessment and decision-making.

A secondary rise in serum hCG after near normalisation or remission suggests a pregnancy or recurrent/ secondary disease. Early differentiation between the 2 conditions may be made by reference to serum progesterone levels, which are raised from follicular phase to luteal levels if the patient is pregnant; and also by vaginal ultrasound which can detect a pregnancy as early as 4 and a half weeks.

The high (22%) percentage of patients who defaulted follow-up clearly emphasises the need to improve measures for detection and recall. The problem may be circumvented in part by adequate early counseling. Identification of patients who may be considered high risk for recurrent disease or prolonged regression would enable special attention to be paid to such a group. To this end, we have related available information such as maternal age, gravidity, gestational age and the first available post-evacuation βhCG titre to the regression time, but found no correlation.

In conclusion, in the absence of universally defined cut-off values which do not exist for obvious reasons, a locally-established reference post-molar hCG regression envelope can be beneficially utilised to identify patients who may need treatment on the basis that:

a. there is a grossly raised serum hCG level for the post-evacuation time;

b. the patient's regression curve overlaid on the regression envelope indicates fluctuations outside the reference domain or raised values persisting in consecutive measurements over 2 to 4 weeks (plateauing); and

c. there is a secondary continuous rise in hCG.

Acknowledgement

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