URINARY EXCRETION OF HUMAN CHORIONIC GONADOTROPHIN IN PATIENTS WITH HYPEREMESIS GRAVIDARUM

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The aetiology of hyperemesis gravidarum has been the subject of much speculation and very little factual information. The possibility that ovarian and placental hormones may play some part has been suggested by various investigators (Anselmino and Hoffmann, 1936; Rakoff, 1940; Schoenck, 1942), but at the time of writing little or no reliable information was available in the literature on the levels of such hormones in the body fluids of patients with this disease.

In a clinical study of a series of patients with hyperemesis gravidarum (Fairweather, 1961, unpublished) the duration of pregnancy at the time of onset of symptoms was noted and it was observed that most subjects presented at a time during pregnancy at which the levels of human chorionic gonadotrophin (H.C.G.) in blood and urine might be expected to be at their maximum. The possibility that patients suffering from hyperemesis might be unduly sensitive to H.C.G. was also considered, and a simple sensitivity reaction was devised to test this hypothesis (see Appendix). The preliminary results obtained suggested that sensitivity to H.C.G. might play some part in the aetiology of the disease, and, accordingly, it was decided to perform urinary H.C.G. assays in a series of patients with hyperemesis gravidarum and to attempt to correlate the assay results obtained with the clinical picture of the disease.

The present report describes studies in a total of 90 patients suffering from hyperemesis gravidarum. The cases were observed in two centres—Aberdeen and Newcastle upon Tyne—by one of us (D. V. I. F.). The study began in November, 1957; the last patient was admitted to the series in March, 1960, and was delivered in October, 1960.

The H.C.G. excretion in the hyperemesis patients was compared with that in a series of normally pregnant women at comparable stages of pregnancy. The "control" subjects were also observed in two centres, in Edinburgh by J. A. L. from 1947 to 1949 and in Newcastle upon Tyne by D. V. I. F. during 1960. The results obtained in the Edinburgh series have been reported previously (Loraine, 1949a, 1950a).

For the purpose of this study hyperemesis gravidarum is defined as vomiting in pregnancy, occurring up to and including the 20th week of gestation, unassociated with conditions coincidental to the pregnancy such as pyelitis, appendicitis, etc., and of such severity as to require the admission of the patient to hospital.

Materials and Methods

Hyperemesis Patients.—As soon as a patient suffering from hyperemesis gravidarum was admitted to hospital one of us (D. V. I. F.) interviewed her and made a clinical assessment. Arrangements were then made for a complete 24-hour urine sample to be collected. If the total volume of the specimen exceeded 500 ml., a 40-ml. aliquot was taken and dispatched to the Clinical Endocrinology Research Unit, Edinburgh, for H.C.G. assay. The total volume of the 24-hour sample was noted, and this figure, together with the code number for the sample, was the only information supplied to the laboratory in Edinburgh. One week later a further 24-hour urine collection was made from the patient, and this specimen too was sent for H.C.G. assay. In a few cases further urine samples were obtained where possible.

Control Subjects.—*Newcastle upon Tyne:* Six patients in their first pregnancy were selected as early as possible in the pregnancy; their ages ranged from 20 to 32 years. Twenty-four-hour specimens of urine were obtained at weekly intervals up to the 20th week of the pregnancy, and thereafter at monthly intervals until delivery. Aliquots were taken and dispatched to Edinburgh as above for H.C.G. assay. None of these patients showed any obstetrical abnormality throughout pregnancy. *Edinburgh:* In five subjects 24-hour urine collections for H.C.G. assay were made at weekly intervals from early pregnancy until the 20th week of gestation. In a further nine subjects isolated determinations were made at various stages of pregnancy. The average age (30 years) was higher than that in the group of normal subjects from Newcastle upon Tyne, and most of the subjects were multiparous.

Method of Assay of H.C.G.—The method of Loraine (1950a) was used. In this technique, the details and reliability criteria of which are described elsewhere, the end-point of the bioassay is the enlargement of the total prostate in intact immature male rats. Untreated urine is employed and results are expressed in terms of the international standard for H.C.G. as I.U. for 24 hours. This method of assay has previously been extensively used in clinical studies (Loraine, 1949b; Loraine and Matthew, 1950, 1953; Diczfalusy, 1953).

Clinical Details of Cases and Outcome

Aberdeen Cases.—There were 70 patients, including one observed in two pregnancies, making in all 71 cases. The ages ranged from 19 to 37 years, the majority (57) being in the 20–30 years range. There were no illegitimate pregnancies, but four patients had pre-nuptial conceptions. The distribution of patients according to parity (pregnancy number) was as follows: first pregnancy, 31; second 18; third, 10; fourth, 9; fifth, 2; sixth, 1. In six cases all previous pregnancies had ended in abortion. Twenty-six (36%) of the women were classified as tall—5 ft. 4 in. (162.5 cm.) and over—and 10 (14%) small—under 5 ft. 1 in. (155 cm.). Three of the pregnancies ended in spontaneous abortion, and in one case the pregnancy was terminated on medical and social grounds. No congenital foetal abnormalities were noted in the series. There were four twin pregnancies, and of the 71 infants 37 were males and 34 females (sex of abortions not recorded). Three stillbirths occurred. Two of these were intrauterine deaths of doubtful cause occurring at the 30th and 37th weeks respectively; one followed a toxic accidental haemorrhage at 30 weeks. Readmission was required once by

nine patients, twice by two, thrice by one, and four times by one on account of recurrent hyperemesis. Thirteen patients gave a history of requiring admission to hospital because of hyperemesis in previous pregnancies. Four patients developed severe pre-eclamptic toxæmia and five mild pre-eclamptic toxæmia. A further four patients showed hypertension only.

Newcastle upon Tyne Cases.—There were 19 patients, ranging in age from 20 to 40 years. One pregnancy was illegitimate. The distribution of patients according to parity (pregnancy number) was as follows: first pregnancy, 5; second, 5; third, 3; fourth, 4; fifth, 1; sixth, 1. In two cases all previous pregnancies had ended in abortion. Six women were classified as tall and four as small. (In six cases the height was not recorded.) No abortions occurred in this series, but one case was found to be an ectopic pregnancy at 13 weeks. No congenital foetal abnormalities were noted. There was one twin pregnancy, and of the 19 infants born 10 were males and 9 females; no stillbirths occurred. Two patients required readmission once and four twice on account of recurrent hyperemesis, and five patients gave a history of admission in previous pregnancies on account of hyperemesis. One patient developed severe, one moderate, and two mild pre-eclamptic toxæmia.

Results

The results of this study are presented in Figs. 1 and 2 and in Tables I-IV. Fig. 1 shows for each week of pregnancy the H.C.G. excretion in both the hyperemesis patients and the normal subjects. Fig. 2 shows the mean values in both hyperemesis and normal groups for three separate stages of pregnancy—namely, 7 to 10 weeks, 11 to 15 weeks, and 16 to 20 weeks. The very low mean figure for H.C.G. excretion in the hyperemesis group for the stage of gestation from 7 to 10 weeks

should be noted. This finding indicates that in patients with this disease the "peak period" of H.C.G. excretion which normally occurs in the first trimester of pregnancy is absent.

Tables I and II present in summary form details of the observations made in the hyperemesis patients from

TABLE IV.—H.C.G. Excretion in Normally Pregnant Women According to Stage of Pregnancy

Centre	Stage of Pregnancy (Weeks)	No. of Subjects	No. of Readings	Mean H.C.G. Excretion (I.U./24 Hours)	Arithmetic Range (I.U./24 Hours)
Newcastle	7-10	4	9	53,400 ± 3,780*	35,000-71,400
Edinburgh	7-10	6	14	29,190 ± 1,890*	18,320-46,000
Total	7-10	10	23	38,680 ± 2,760*	18,320-71,400
Newcastle	11-15	6	27	37,780 ± 1,360*	11,520-82,810
Edinburgh	11-15	9	26	11,410 ± 1,400*	4,500-32,740
Total	11-15	15	53	19,760 ± 2,200*	4,500-82,810
Newcastle	16-20	6	25	9,120 ± 640*	4,830-18,130
Edinburgh	16-20	9	19	6,760 ± 320*	4,500-9,350
Total	16-20	15	44	8,090 ± 420*	4,500-18,130

* Standard error of the mean.

Fig. 1.—Urinary excretion of H.C.G. in normal pregnancy and hyperemesis gravidarum.

Fig. 2.—Mean H.C.G. excretion at various stages of pregnancy.

TABLE I.—H.C.G. Excretion in Patients with Hyperemesis Gravidarum Throughout Pregnancy

Centre	Stage of Pregnancy (Weeks)	No. of Subjects	No. of Readings	Mean H.C.G. Excretion (I.U./24 Hours)	Arithmetic Range (I.U./24 Hours)
Aberdeen	7 onwards	71	140	10,850 ± 1,230*	900-113,100
Newcastle	"	19	39	8,220 ± 550*	2,000-18,400
Total	"	90	179	10,270 ± 1,020*	900-113,100

* Standard error of the mean.

TABLE II.—H.C.G. Excretion in Patients with Hyperemesis Gravidarum According to Stage of Pregnancy

Centre	Stage of Pregnancy (Weeks)	No. of Subjects	No. of Readings	Mean H.C.G. Excretion (I.U./24 Hours)	Arithmetic Range (I.U./24 Hours)
Aberdeen	7-10	34	52	12,980 ± 3,000*	2,000-113,100
"	11-15	40	69	8,960 ± 910*	1,600-43,200
"	16 onwards	10	19	12,540 ± 3,520*	900-59,200
Aberdeen + Newcastle	7-10	44	71	12,130 ± 2,110*	2,000-113,100
"	11-15	49	86	8,880 ± 650*	1,600-43,200
"	16 onwards	12	22	11,510 ± 3,000*	1,000-59,200

* Standard error of the mean.

TABLE III.—H.C.G. Excretion in Normally Pregnant Women Throughout Pregnancy

Centre	Stage of Pregnancy (Weeks)	No. of Subjects	No. of Readings	Mean H.C.G. Excretion (I.U./24 Hours)	Arithmetic Range (I.U./24 Hours)
Newcastle	7-20	6	61	23,920 ± 2,540*	4,830-82,810
Edinburgh	7-20	14	59	14,130 ± 1,350*	4,500-46,000
Total	7-20	20	120	19,110 ± 1,280*	4,500-82,810

* Standard error of the mean.

Aberdeen and Newcastle upon Tyne. Corresponding information for the normal subjects from Newcastle upon Tyne and Edinburgh is shown in Tables III and IV.

Analysis of Results

The mean H.C.G. excretion from the seventh week of pregnancy onwards in the group of hyperemesis patients from Aberdeen was 10,850 I.U. per 24 hours (Table I). This figure did not differ significantly from the corresponding value for the group of hyperemesis cases from Newcastle upon Tyne ($P>0.2$). The larger standard error of the mean and the wider arithmetic range in the Aberdeen as compared with the Newcastle upon Tyne series should be noted. This is accounted for by the presence in the Aberdeen series of three patients in whom H.C.G. readings were much higher than in the other 68 Aberdeen patients or in any of the subjects from Newcastle upon Tyne. In these three patients, who did not differ clinically from any of the others in the group, H.C.G. excretion values ranged from 43,200 to 113,100 I.U. per 24 hours. Because of the non-orthogonal distribution of the data on the hyperemesis patients it was not possible to analyse the results separately for factors such as the age, parity, and height of the mother, the sex and weight of the child, and the duration of stay in hospital.

The mean H.C.G. excretion from the 7th to the 20th weeks in the normal subjects from both Edinburgh and Newcastle upon Tyne was 19,110 I.U. per 24 hours (Table III). This figure was significantly higher than that for the combined mean of the Aberdeen and Newcastle upon Tyne hyperemesis patients ($P<0.001$). In the periods of gestation from 7 to 10 weeks and from 11 to 15 weeks (Table IV) the mean excretion in the normal subjects was significantly higher than that in the hyperemesis patients ($P<0.001$ for both groups), but in the period from 16 weeks onwards a significant difference was not observed ($P>0.1$).

At all stages of pregnancy the mean H.C.G. excretion in the group of normal subjects from Newcastle upon Tyne was significantly higher than that from the normal subjects in Edinburgh ($P<0.001$ for the periods of gestation 7 to 20 weeks, 7 to 10 weeks, and 11 to 15 weeks; $P<0.01$ for the period 16 to 20 weeks). This finding is difficult to explain but may be due to the fact that the Newcastle upon Tyne series consisted entirely of young primigravid subjects, while the Edinburgh series was mainly composed of older multi-gravid subjects.

Discussion

The pattern of excretion of H.C.G. throughout normal pregnancy is now well established (see Loraine, 1958). Very large quantities of H.C.G. appear in the urine in the first trimester of pregnancy, and this constitutes the so-called "peak period" of excretion of the hormone. Readings obtained at this time are very variable from one individual to another and range from 20,000 to 100,000 I.U. per 24 hours. The time at which H.C.G. readings begin to decrease is also very variable, but in most subjects the peak period has passed by the 15th week of pregnancy. In the second and third trimesters of pregnancy the urinary excretion values are much more constant than in early pregnancy, and at this time readings are generally below 11,000 I.U. per 24 hours (Loraine, 1950a).

The present study has demonstrated that in patients with hyperemesis gravidarum the mean H.C.G. excretion

from the 7th to the 15th week of pregnancy is significantly lower than that in normally pregnant women. This discrepancy is especially marked in the period of gestation extending from 7 to 10 weeks (Fig. 2), and the findings at this stage of pregnancy indicate that in hyperemesis patients the normal "peak period" of H.C.G. excretion is absent. The data in this investigation are contrary to those reported by Schoeneck (1942), who claimed that in patients with this disease the concentration of H.C.G. in urine was higher than that in normal pregnant women at a comparable stage of gestation. The reason for these conflicting findings can probably be explained on a methodological basis. In Schoeneck's study H.C.G. was assayed in urine by a modified Friedman test, and it is now well recognized that this method has severe limitations from the quantitative point of view. Moreover, Schoeneck's results were calculated as concentrations rather than as 24-hour excretion values, and it is now generally agreed that this mode of expression of results, which takes no account of the volume of urine excreted daily, is unsatisfactory. This latter criticism is of particular importance in patients with hyperemesis gravidarum, many of whom show a marked degree of oliguria.

It is not at present clear why the H.C.G. excretion in the series of patients with hyperemesis gravidarum should be lower than that in normal pregnant women. One possibility might be that these patients were usually in poor general condition and were hospitalized throughout, whereas the normal subjects were ambulant during the whole period of study. Apostolakis and Loraine (1960) have noted that in the case of human pituitary gonadotrophins mean values both in urine and in plasma are significantly higher in ambulant subjects than in hospitalized patients suffering from various diseases, and it is possible that the excretion of H.C.G. is affected in a similar manner. The actual mechanism which operates in the body to cause the abnormally low urinary H.C.G. levels in hyperemesis is completely unknown. Presumably there might be a selective failure of H.C.G. production by the placenta or, alternatively, an increased utilization of the hormone by the peripheral tissues. Another possibility is that the diminished excretion of H.C.G. might be due to renal damage producing a diminished renal clearance of the hormone and a decreased urinary output. The fact that renal damage in association with oliguria can cause abnormalities in the handling of H.C.G. by the kidney is shown by the previous observation (Loraine, 1950b) that in patients with severe pre-eclamptic toxæmia the mean H.C.G. clearance is significantly lower than in normal pregnancy.

The present investigation has shown that from the 7th to the 20th week of pregnancy the mean H.C.G. excretion in the normal subjects from Newcastle upon Tyne was significantly higher than in the normal subjects from Edinburgh. This difference between cities is at first sight difficult to explain, but it is possible that factors such as the age and parity of the subjects may have been responsible, in view of the fact that the series from Newcastle upon Tyne were a carefully selected group of young women in their first pregnancy, whereas the series from Edinburgh consisted mainly of older multiparous women. Investigations are at present in progress to determine the effect of age and parity on H.C.G. excretion in normal pregnancy, and the results will be reported subsequently.

Summary

Urinary H.C.G. assays have been performed in 90 patients with hyperemesis gravidarum and the results have been compared with those in a series of 20 normally pregnant women. The hyperemesis patients were observed in Aberdeen and in Newcastle upon Tyne and the normal subjects in Newcastle upon Tyne and in Edinburgh.

The mean H.C.G. excretion from the seventh week of pregnancy onwards in the hyperemesis patients from Aberdeen did not differ significantly from the corresponding value in the Newcastle upon Tyne cases.

From the 7th to the 15th week of pregnancy the mean H.C.G. excretion in the hyperemesis patients was significantly lower than that in the normally pregnant women. From the 15th to the 20th week of pregnancy a significant difference between the two groups was not observed.

At all stages of pregnancy investigated the mean H.C.G. excretion of the group of normal subjects from Newcastle upon Tyne was significantly higher than that in the series of normal subjects from Edinburgh.

In the performance of the H.C.G. assays the skilled technical assistance of Miss M. A. Mackay and Miss K. Bach-Pedersen was much appreciated. We are also indebted to the nursing staffs at all the hospitals concerned, and in particular to Miss M. Grassick and Sister C. M. Campbell, from Aberdeen Maternity Hospital, for their assistance in collecting and dispatching samples.

APPENDIX

Pregnyl Sensitivity Test

One ampoule of "pregnyl" (human chorionic gonadotrophin B.P.) is made up with the diluting fluid supplied. The solution is well mixed and drawn up into a tuberculin syringe. An area on the patient's forearm is cleaned. An intradermal injection of 0.05 ml. of the pregnyl is then given into the prepared arm.

A positive reaction is indicated by the appearance immediately or within 24 hours of a red weal or flare round the area of the injection.

In the first 25 hyperemesis cases tested there were 20 positive results. In 35 control cases there were only five positive results. Subsequent correlation appeared to show that severe reactions tended to occur in patients in whom the H.C.G. level in urine was high.

Continued trial of the test, however, showed it to be unreliable because the extent of the reaction was extremely variable from one subject to another and because ultimately no definite correlation was found between the reaction and the H.C.G. level in urine. In view of these findings the test was discontinued in July, 1958.

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SALICYLATES AND GASTRO- INTESTINAL BLEEDING

ACETYSALICYLIC ACID AND ASPIRIN DERIVATIVES

BY

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The association between aspirin and haemorrhagic lesions of the gastro-intestinal tract has been observed by a number of investigators (Douthwaite and Lintott, 1938; Muir and Cossar, 1955; Alvarez and Summer-skill, 1958). The detection of occult blood in the stools of people taking salicylates by mouth was first recorded by Gregerson (1916). More recent investigations have extended this observation—chemical estimations (Lange, 1957; Stubbé, 1958); radioactive chromat studies (Scott *et al.*, 1961, reviewing the subject in some detail)—and have shown that approximately 70% of people bleed after taking aspirin. These findings initiated a search for a compound with all the valuable analgesic and anti-inflammatory properties of aspirin and which was free from associated gastro-intestinal blood loss. The present paper describes our findings with a number of preparations and derivatives of aspirin.

Material and Methods

Aspirin Preparations

The aspirin derivatives examined are listed in Table I, and Fig. 1 depicts their structural formulae. Further details of the less common preparations are given below. Some preparations were "buffered," and so the amount of acid required to restore the pH of a solution of the preparation to that of a saturated solution of acetyl-

FIG. 1.—Structural formulae of principal aspirin compounds examined.

salicylic acid is included in Table I as a measure of the antacid properties of the different formulations. In most instances studies were conducted by administering 15 gr. (972 mg.) of aspirin B.P. or its equivalent four times daily after food, usually for five days. Lower dosage was occasionally necessary because of salicylism, but all comparisons were made with equivalent doses

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