URINARY FORMIMINO-GLUTAMIC ACID EXCRETION IN PREGNANCY

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Formimino-glutamic acid is a metabolite in the pathway of the breakdown of the amino-acid histidine to glutamic acid. A competent folic-acid coenzyme is the acceptor of the formimino group in this pathway, and the compound formimino-glutamic acid therefore accumulates when there is interference with folic-acid function. In practice the urinary excretion of formimino-glutamic acid is measured after an oral dose of 15 g. of histidine hydrochloride, and normal subjects excrete 1 to 17 mg. of this substance in the urine (mean 9 mg.). An excretion in excess of this is usually found in patients with megaloblastic anaemia requiring treatment with folic acid (Luhby, Cooperman, and Teller, 1959).

There is evidence that folic-acid deficiency often develops during the course of normal pregnancy. Thus the rate of clearance from the plasma of intravenously injected folic acid becomes more rapid as pregnancy progresses (Chanarin, MacGibbon, O'Sullivan, and Mollin, 1959) and the serum *Lactobacillus casei* activity falls (Solomons, Lee, Wasserman, and Malkin, 1962). This paper reports the results of a survey of folic-acid deficiency in normal pregnancy, using the urinary excretion of formimino-glutamic acid as the index of folic-acid function.

Materials and Methods

Formimino-glutamic acid was estimated spectrophotometrically by the method of Chanarin and Bennett (1962).

Forty-five pregnant subjects less than 16 weeks pregnant, attending the antenatal clinic at St. Mary's Hospital, London, were given 15 g. of histidine orally and the urine for eight hours was collected into a polythene bottle to which had been added 2-3 ml. of N/HCl. The test was repeated on the same patients at 20, 30, 35, and 39 weeks, and on day 6 after delivery. For various reasons we were able to repeat the test on only 40 of the subjects at 35 weeks and on 30 subjects at 39 weeks. An aliquot of the urine was stored at -20°C . until assayed.

Results

The results of the urinary excretion of formimino-glutamic acid are shown in the Chart. The urinary excretion before the 16th week of pregnancy varied from 0 to 156 mg., with a mean of 21 mg. The excretion was elevated above the normal range in 16 of these subjects (36%). Thereafter the excretion fell, the means being 14 mg. at 20 weeks, 10 mg. at 30 weeks, 7 mg. at 35 weeks, and 8 mg. at 39 weeks. Similarly the number of subjects excreting more than 17 mg. of formimino-glutamic acid during the test fell from 13 (29%) at 20 weeks and 8 (18%) at 30 weeks to 2 (5%) at 35 weeks. The excretion rose in the puerperium (mean 17 mg.), and 15 tests (33%) were above the range found in non-pregnant subjects at this time.

Discussion

Unlike other tests for folic-acid deficiency, such as the folic-acid clearance or the assay of serum *L. casei* activity,

the urinary excretion of formimino-glutamic acid does not provide evidence for the development of folic-acid deficiency in pregnancy. It has been shown that the urinary excretion of formimino-glutamic acid is an unsatisfactory test for folic-acid deficiency in pregnancy and is within normal limits in half the patients with megaloblastic anaemia in pregnancy (Chanarin, Rothman, and Watson-Williams, 1963). Husain, Rothman, and Ellis (1963) have also shown that urinary formimino-glutamic acid may be present at 28 weeks in some patients but be absent in later pregnancy.

A number of factors are responsible for the unsatisfactory nature of urinary formimino-glutamic acid excretion as a test of folic-acid function in pregnancy. There is a slow prolonged absorption of histidine from the gastrointestinal tract and at the same time an excretion of up to 6 g. of the dose of histidine into the urine (Chanarin *et al.*, 1963). The urinary loss of histidine is due to a lowered renal threshold (Page, Glendening, Dignam, and Harper, 1954). However, these factors are relatively constant throughout pregnancy and do not explain the declining

Urinary excretion of formimino-glutamic acid in 45 pregnant subjects after an oral dose of 15 g. of histidine hydrochloride. The upper limit of excretion in non-pregnant subjects is 17 mg. (continuous line) with a mean excretion of 9 mg. The mean excretion in each group is indicated as the hatched area and is 21 mg. before the 16th week, 14 mg. at 20 weeks, 10 mg. at 30 weeks, 7 mg. at 35 weeks, 8 mg. at 39 weeks, and 17 mg. on day 6 after delivery.

excretion of formimino-glutamic acid as pregnancy advances. The fall in formimino-glutamic acid excretion rather implies that with the increasing growth-rate of the foetus an increasingly large amount of histidine is being used for protein synthesis, and therefore less of the amino-acid follows the catabolic pathway leading to formimino-glutamic acid and glutamic acid.

Summary

The urinary excretion of formimino-glutamic acid was measured after an oral dose of 15g. of histidine in 45 pregnant subjects in early pregnancy and again at 20, 30,

35, and 39 weeks, and after delivery. Unlike other tests for folic-acid deficiency, which often give abnormal results in pregnancy, there is a steady decline in the amount of formimino-glutamic acid excreted in the urine throughout pregnancy. It is suggested that this is due to the utilization of increasing amounts of histidine for protein synthesis in pregnancy.

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REFERENCES

- Chanarin, I., and Bennett, M. C. (1962). *Brit. med. J.*, **1**, 27.
 — MacGibbon, B. M., O'Sullivan, W. J., and Mollin, D. L. (1959). *Lancet*, **2**, 634.
 — Rothman, D., and Watson-Williams, E. J. (1963). *Ibid.*, **1**, 1068.
 Husain, O. A. N., Rothman, D., and Ellis, L. (1963). *J. Obstet. Gynaec. Brit. Cwlth*. In press.
 Lohby, A. L., Cooperman, J. M., and Teller, D. N. (1959). *Proc. Soc. exp. Biol. (N.Y.)*, **101**, 350.
 Page, E. W., Glendening, M. B., Dignam, W., and Harper, H. A. (1954). *Amer. J. Obstet. Gynec.*, **68**, 110.
 Solomons, E., Lee, S. L., Wasserman, M., and Malkin, J. (1962). *J. Obstet. Gynaec. Brit. Cwlth*, **69**, 724.

PORTAL PHLEBOTHROMBOSIS IN THE PUERPERIUM: A REPORT OF THREE CASES

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Mesenteric vascular occlusion has long been recognized as a cause of infarction of both small and large bowel. It was not, however, until the work of Warren and Eberhard (1935) that the venous type was clearly differentiated from the arterial and accepted as a distinct clinical entity. It invariably takes the form of thrombosis in the portal system and has been classified clinically (Skandalakis, 1958) as primary (idiopathic) or secondary. Few cases, however, will be regarded as idiopathic if all the possible aetiological factors are carefully assessed.

However, infarction of bowel resulting from thrombosis in the portal system during pregnancy and the puerperium has very rarely been reported, and only 11 cases were found in a review of the world literature. Of these, four followed abortions, two occurred during pregnancy, and four during the puerperium. One case was not proved. Only two cases seem to have been definitely primary in nature (Bucura, 1923; Heimrath, 1961). No survivors were reported.

Three further cases of portal phlebothrombosis during the puerperium are here presented.

Case 1

A housewife aged 27 attended the antenatal clinics of the Southampton Group of Hospitals during her third pregnancy in 1961. Her two previous pregnancies had terminated in abortion—the first in 1958 at 24 weeks and the second in 1960 at 8 weeks.

The third pregnancy was uneventful. Her haemoglobin was recorded as 83% on booking. She was admitted to the Southampton General Hospital at 38 weeks, and after a normal labour lasting 13 hours was delivered of a living female infant weighing 5 lb. (2.270 g.). The placenta was expressed after five minutes and the total blood loss did not exceed 300 ml.

The puerperium was uneventful and her haemoglobin was 71% on the fifth day. The child did not regain its birth weight until the 12th day after delivery, and the patient therefore remained in hospital. On the 17th day, when about to be discharged, she complained of continuous abdominal pain, which she said had been gradually worsening for 48 hours. That morning she had passed two loose stools of normal colour, and vomited her breakfast. She appeared well, but her temperature had risen to 99.4° F. (37.4° C.) and her pulse rate to 100. On examination there was definite tenderness with some guarding in the epigastrium and around the umbilicus, but there was no rebound tenderness and normal bowel sounds were heard. On vaginal examination the uterus was found to

be well involuted. The symptoms and signs remained unchanged during the day, but that evening the abdominal pain became generalized and much more severe, and several times she vomited bile-stained fluid. During two hours the pulse rate rose to 120, the blood-pressure fell from 120/80 to 90/50, and she was noted to be pale, cold, and sweating. Considerable abdominal distension was obvious and there were generalized guarding, tenderness, and rebound tenderness. No bowel sounds were to be heard.

An intravenous infusion of plasma was begun, gastric suction was carried out, and 500 ml. of blood-stained fluid was aspirated. After 1,500 ml. of plasma and 1,200 ml. of blood had been transfused her condition had improved sufficiently for laparotomy to be undertaken.

On opening the abdomen a large quantity of blood-stained fluid escaped, and numerous distended coils of small bowel of a dark reddish-black colour were seen. Patchy discoloration was found to commence about 2 feet (60 cm.) from the duodeno-jejunal flexure, and it was obvious that the distal jejunum, ileum, and caecum had undergone infarction. As normal pulsation was felt in the superior mesenteric artery and its branches, this was thought to be the result of venous thrombosis. The area of involved bowel was so extensive that resection was not thought practicable and the abdomen was closed.

Despite massive blood and plasma infusion, intravenous heparin, close electrolyte control, and, ultimately, intravenous hydrocortisone and noradrenaline drip, the patient's condition steadily deteriorated and she died 48 hours later.

At necropsy the abdomen was distended. Small bilateral serous effusions were present in the pleural cavities. The peritoneal cavity contained a blood-stained effusion and the surfaces of the lower jejunum, ileum, and caecum were dull, dark red in colour, and covered with a fibrinous exudate. A firm thrombus occluded the superior mesenteric and portal veins (Fig. 1). The vein walls appeared healthy. There was diffuse fatty infiltration of the liver parenchyma. Several pancreatic veins were occluded by thrombus, but no sign of pancreatitis was present. The uterus showed normal involution with no sign of inflammation, and the uterine veins were patent.

Case 2

A married woman aged 22 attended her own doctor during her fourth pregnancy in 1951. Her previous confinements had been normal.

On August 9, 1951, she had a normal delivery at home of a living full-term infant after a short labour. The puerperium was quite uneventful until the 13th day, when she had abdominal pain. This continued intermittently for 48 hours; it then became much more severe and she passed blood per

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