Folic Acid Absorption in Pregnancy: Comparison of the Pteroylpolyglutamate and Pteroylmonoglutamate

By FREDERICK W. MCLEAN, M. WAYNE HEINE, BEREL HELD AND RICHARD R. STREIFF

The gastrointestinal absorption of naturally occurring folate (pteroylpolyglutamate) and therapeutic folate (pteroylmonoglutamate) was studied in a series of pregnant subjects. No significant difference in absorption was found. Furthermore, the elevated estrogen and progesterone levels which occur during pregnancy do not inhibit absorption of pteroylpolyglutamate.

IT IS REASONABLE TO ASSUME that the demands of the fetus, as well as the increased needs of the mother, might lead to folate deficiency in certain pregnant women. There is also however, another aspect of the problem which has received minimal attention: i.e., an alteration in the absorption of folate.

After Streiff presented evidence suggesting the inhibition of pteroylpolyglutamate absorption by oral contraceptives,1 we focused our attention upon the problem of folate absorption as it relates to pregnancy. We reasoned that if the small amounts of estrogen and progestin peculiar to the oral contraceptive would alter pteroylpolyglutamate absorption, what then would be the effect of the much larger quantities of estrogen and progesterone produced during gestation? The data obtained form the substance of this report.

MATERIALS AND METHODS

Nine volunteers were selected from our prenatal clinic. Most of the gravidas were in the last half of pregnancy and were considered uncomplicated. Malabsorption was not suggested by their histories. Although some of the individuals had been taking prenatal vitamins (Pre-Enthus, S. J. Tutag and Co.) containing 100 µg. of pteroylmonoglutamate (asterisked in Table 1) the medication was discontinued at least 24 hours before the institution of the investigation.

The pteroylpolyglutamate was prepared by a modification of the method described by Greene.2 This modification consisted of mixing the yeast and 70 per cent ethanol in a large
Table 1.—Serum Values Following the Ingestion of Folic Acid

<table>
<thead>
<tr>
<th>Patient</th>
<th>200 µg. of Pteroylpolyglutamate</th>
<th>200 µg. of Pteroylmonoglutamate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hour 1.0 hour 2.5 hour</td>
<td>0 hour 1.0 hour 2.5 hour</td>
</tr>
<tr>
<td>D. B.</td>
<td>4.2 7.5 7.3</td>
<td>4.0 4.7 6.4</td>
</tr>
<tr>
<td>B. H.</td>
<td>2.6</td>
<td>6.2</td>
</tr>
<tr>
<td>E. C.</td>
<td>6.4</td>
<td>9.9</td>
</tr>
<tr>
<td>G. H.</td>
<td>20.5</td>
<td>25.7</td>
</tr>
<tr>
<td>G. B.*</td>
<td>29.3</td>
<td>37.0</td>
</tr>
<tr>
<td>L. E.*</td>
<td>15.9</td>
<td>20.6</td>
</tr>
<tr>
<td>R. C.*</td>
<td>9.1</td>
<td>18.6</td>
</tr>
<tr>
<td>A.L.*</td>
<td>8.8</td>
<td>16.1</td>
</tr>
<tr>
<td>C.B.*</td>
<td>11.1</td>
<td>10.4</td>
</tr>
<tr>
<td>Mean</td>
<td>12.0</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Mean increase above base

|         | 6.2 | 5.2 | 3.9 | 4.9 |

* Prenatal vitamins.

beaker rather than using a column. Pteroylpolyglutamate obtained in this manner was de-conjugated to the monoglumatic form and then assayed microbiologically. The pteroyl-monoglutamate solution was prepared by diluting the therapeutic preparation (Folvite, Lederle Laboratories) to a concentration of 200 µg./ml. Thus, the molarity of pteroylpolyglutamate and pteroylmonoglutamate given the subjects was equal.

The patients were studied between 9 a.m. and 1 p.m. in the fasting state. After a baseline serum folate was obtained, each patient was given 200 µg. of the solution by mouth. Absorption of pteroylpolyglutamate was studied on day 1; 24 hours later, the pteroylmonoglutamate investigation was begun. All of the volunteers remained in a fasting state until both the 1 hour and 2½ hour post-ingestion samples were collected.

Serum folate was assayed by the technique of Herbert.3 Twenty-four hour urinary estriol concentration was determined in all patients by the method of Scommegna and Chattoraj.4 In addition to a dietary history, a serum carotene level was determined on each patient. Although this is a relatively insensitive test of malabsorption, we employed it as a screen to help exclude a nonspecific malabsorption problem.

**RESULTS**

As shown in Table 1, there were comparable serum folate elevations after ingestion of both the pteroylpolyglutamate and the pteroylmonoglutamate. In the pteroylpolyglutamate absorption study, a mean serum folate increase of 6.2 mg./ml. occurred at 1 hour and a mean 5.2 mg./ml. rise was noted at 2½ hours. By comparison, in the pteroylmonoglutamate series, the mean 1 hour rise above baseline was 3.9 mg./ml. and the mean 2½ hour increase was 4.9 mg./ml.

All estriol determinations were found to be in the normal range for a given duration of gestation. Serum carotene levels and hematocrits are seen in Table 2. In no instance were carotene values below the normal range. The hematocrits were within the normal range of our prenatal patients. Of particular interest was patient B. H., who was the only individual to have a low serum folate; her hematocrit was 41 volume per cent.

**DISCUSSION**

Impaired absorption of folate during pregnancy may serve as a contributing
factor in the development of overt megaloblastic anemia and of lesser degrees of folate depletion. For example, Giles found evidence of decreased uptake of orally administered folic acid and suggested impaired intestinal absorption as an important contributory factor in megaloblastic anemia complicating pregnancy. Additional patients have been studied in which the etiology of megaloblastic anemia during pregnancy was attributed to intestinal malabsorption secondary to early tropical sprue. Megaloblastosis developing in individuals with a single pregnancy who were eating a normal diet and who were free of vomiting and diarrhea prompted Girdwood to question the mechanisms of folate deficiency. He suggested that in some pregnancies, an abnormal steroid or some other metabolite interfered with folic acid metabolism; he was unclear as to the exact mode of action.

It has been suggested that there is usually decreased motility of the gastrointestinal tract and prolonged gastric emptying time during pregnancy. Hence, a direct comparison of gastrointestinal absorption between pregnant and nonpregnant individuals is difficult. With the gravida serving as her own control, however, it was felt that a meaningful comparison could be established between the absorption of the pteroylpolyglutamate and pteroylmonoglutamate.

Another matter of concern in such investigations relates to blood volume and, more specifically, the plasma volume increases which occur in pregnancy. The point to be made here is that we are determining a relative concentration in the plasma and not an absolute amount of folate absorbed through the gastrointestinal tract. Our study on each gravida was completed within 2 days, so it would be unlikely to find a significant alteration in the plasma volume during this interval.

We felt our normal urinary estriol values important because of the previous association reported between reduced urinary estrogen excretion and low serum folate activity. Our observation of normal levels of urinary estriol associated with normal serum folate levels does not contradict that report.

It appears then, that the absorption of pteroylpolyglutamate and the absorption of pteroylmonoglutamate are similar. The hormonal alterations found in pregnancy do not selectively change pteroylpolyglutamate absorption as was found in the study of oral contraceptives. This would suggest that as they
relate to folate absorption, oral synthetic estrogens and progestins may act in a different manner than the naturally occurring hormones.

REFERENCES


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