Pyridoxine Supplementation During Pregnancy

Clinical and Laboratory Observations

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SUBSTANTIAL laboratory evidence continues to suggest an alteration of vitamin B_6 metabolism during pregnancy. Although contents of this substance in blood, skin and urine are not regularly reduced in gravid women,[1-3] the elimination of 4-pyridoxic acid following pyridoxal administration is commonly below the normal range.[4] Impairment of vitamin B_6-dependent aspects of protein metabolism also has been inferred from altered urinary patterns of breakdown products, notably those induced by the administration of test loads of amino acids and those prevented by the administration of relatively small amounts (5 to 10 mg.) of this substance.[1,5-11]

Although some of these apparent aberrations have seemed more common among patients with toxemia, their specific mechanisms and clinical implications remain to be elucidated. It has been reported that the administration of pyridoxine supplements has reduced the frequency of pre-eclampsia[12] and of placental vascular sclerosis in pregnant women,[13] as well as of convulsive seizures in vitamin B_6-depleted and/or dependent infants.[14-16] Although these findings have prompted recommendations to prescribe pyridoxine routinely to pregnant women, relevant clinical observations thus far appear too few and too inconclusive to establish the wisdom of such a procedure. The present clinical trial, including selected laboratory procedures, is intended to provide further, practical information concerning the effects of administering vitamin B_6 during the prenatal period.

MATERIAL AND METHODS

The subjects for this study were taken from the ward maternity service of a voluntary hospital which serves an urban community with mixed ethnic representation. A total of 1,532 consecutive patients were assigned at random to one of three groups, with specific vitamin-mineral supplement regimens maintained until delivery. All clinic patients were invited to participate in the study, irrespective of parity or stage of gestation. Group assignments were made at random among the great majority (virtually all) who volunteered to take the supplements. Losses to the study resulted chiefly from transfer of patients to private care and from precipitate delivery outside the hospital. Possible intolerance of the medication was reported infrequently, although appreciable attrition occurred in respect to the special laboratory procedures.

Each vitamin-mineral capsule used in this study contained 6,000 I.U. of vitamin A, 400 units of vitamin D, 1.5 mg. of thiamine, 2.0 mg. of riboflavin, 15.0 mg. of niacin, 5.0 mg. of pantothenic acid, 1.0 mg. of vitamin B_{12}, 0.25 mg. of folic acid, 100.0 mg. of ascorbic acid, 0.20 mg. of sodium iodate, and 15.0

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mg. of ferrous iron. Pyridoxine (20 mg.) was added only to the capsules given to the patients in group 2.

Group 1 consisted of 576 patients who received one vitamin-mineral capsule plus three placebo lozenges daily. Group 2 consisted of 588 patients who received one vitamin-mineral capsule (containing in addition 20 mg. pyridoxine) plus three placebo lozenges daily. Group 3 consisted of 368 patients who received one vitamin-mineral capsule plus three lozenges containing pyridoxine (6.67 mg. each) daily. (The relatively small size of group 3 was attributable to the later subdivision of group 2 (with simultaneous addition of the placebo lozenges for the subjects in groups 1 and 2) in the interest of a related study of the effects of pyridoxine administration on the dental caries experience of pregnant women, which included many of these patients and is the subject of a separate report.[24])

Food intake was not controlled, but general antepartum (and intrapartum) management, including diet instruction, was otherwise uniform. In the absence of complications, patients were observed at four-week intervals until the final trimester, when biweekly or more frequent visits were scheduled.

Employing the double blind technic, comparisons were made between the major study groups, as well as between more uniform subgroups of each of these (group 1, 471; group 2, 448; group 3, 294), comprised of patients who had undergone at least seventy days of treatment and in which ethnic representation, mean age and duration of therapy were virtually identical. Standardized clinic and hospital records were analyzed for the frequency of complications, as well as for the occurrence of other commonly adopted parameters of pregnancy and parturition, e.g., general, subjective complaints (loss of well-being); anorexia; poor food intake; emesis; edema; staining; increased systolic pressure; increased diastolic pressure; and the need for transfusion. The occurrence of prematurity, as well as birth weight and length were also assessed among the members of each group.

Toxemia and other maternal, as well as fetal, complications were credited as diagnosed by the respective attending physician. Separate evaluations of single criteria (e.g., hypertension, proteinuria) provided more objective assessments to supplement these over-all clinical impressions. Eclampsia did not occur in any of the patients in this study. Toxemia was recorded in 2.1 per cent of those in group 1, 3.6 per cent of those in group 2 and in 3.0 per cent of those in group 3, differences which were not significant at the 5 per cent level.

In addition to routine hemoglobin measurements and urinalyses carried out on all patients, the levels of pyridoxal phosphate in the blood (method of Boxer et al.[17]) and, because of the apparent influence of vitamin B_6 on these moieties,[18,19] of serum cholesterol (modified method of Bloor[20]) and serum transaminase (method of Cabaud et al.[21]) were determined in every fifth patient. The tryptophan load test (method of Wachstein and Guaditis[22,23]) was performed in every tenth patient.

RESULTS

In general, the clinical patterns of the patients who received the pyridoxine supplements resembled those of the control subjects. With the exception of the lower prevalence of "poor appetite" noted among the subjects receiving vitamin B_6, differences in respect to the fetal and maternal parameters measured were not statistically significant at the 5 per cent level. Comparable experiences were noted in both the over-all study groups and in the smaller, more homogeneous subgroups.

There were no significant differences in respect to blood hemoglobin concentrations, serum cholesterol and transaminase levels, or in the occurrence of proteinuria. However, the proportion of patients who exhibited mellituria during pregnancy was significantly greater ($P < 0.001$) in group 2 than in group 3; the frequency in group 1 was intermediate.

More predictable, mean vitamin B_6-phosphate levels in the blood were significantly higher among the subjects who received this substance—in the over-all group comparisons as well as among the subsamples. The frequency of abnormal results (excess xanthurenic acid) of the tryptophan load tests among the patients who received the supplement was less—a difference which was statistically significant between the larger, but not the smaller, samples.

COMMENTS

These results do not provide support for a hypothesis that the routine administration of pyridoxine supplements to gravid women induces a more favorable outcome of pregnancy. Although the group who received the supplement had comparatively higher blood levels of vitamin B_6 and, as previously noted by

Wachstein and others, lower levels of xanthurenic acid in the urine following tryptophan ingestion, no clinical corollaries of these observations are apparent. In contrast to the relatively favorable dental experience previously noted among some of these women who received the vitamin B_6 supplement,[24] laboratory significance here is yet to be equated with obstetrical and pediatric significance.

Conceivably, the criteria employed in this study are too conventional and too crude to permit identification of more subtle, but possibly more meaningful clinical effects. A larger sample size also might yield statistically significant differences between groups receiving supplements and those not receiving supplements of pyridoxine.

Although the subjects of the present study represent principally low income and public assistance groups, it is possible, too, that the prevailing state of nutrition, including vitamin B_6, was above the marginal level required for demonstrating beneficial effects from added pyridoxine—at least in the dose and forms employed. Although it is not unreasonable to suspect that pregnancy, in common with other so-called stress situations,[25] may be associated with increased requirements for pyridoxine, the obstetric value of administering supplements of this substance to ostensibly healthy, prenatal patients, remains to be established.

SUMMARY

In a double blind, clinical trial, pyridoxine supplements (20 mg. daily) were administered to 956 pregnant women, who, together with 576 prenatal control subjects, also received a specially formulated multivitamin-mineral preparation and general dietary instruction.

Standardized clinical and hospital records were assessed for possible influence of the vitamin B_6 supplement on the frequency of complications, as well as other commonly adopted parameters of pregnancy. Selected laboratory procedures also were performed for evidence of metabolic effects.

Although the laboratory studies, in common with the dental experience previously noted in some of these patients, indicated differences induced by pyridoxine, no other significant clinical benefits could be attributed to the administration of this substance.

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REFERENCES

1. Friedman, B. I., Becker, L., Thompson, C. and Vilter, R. W. Vitamin B_6 metabolism in the post-partum period. *J. Lab. & Clin. Med.*, 46: 817, 1955.
2. Wachstein, M., Kellner, J. D. and Ortiz, J. M. Pyridoxine PO 4 in plasma and leukocytes of normal and pregnant subjects following B_6 load tests. *Proc. Soc. Exper. Biol. & Med.*, 103: 350, 1960.
3. Diding, N. A. and Melander, S. E. J. Serum vitamin B_6 level in normal and toxemia pregnancy. *Acta obst. et gynec. scandinav.*, 40: 252, 1961.
4. Wachstein, M. and Guaditis, A. Disturbance of vitamin B_6 metabolism in pregnancy. III. Abnormal vitamin B_6 load test. *Am. J. Obst. & Gynec.*, 66: 1207, 1953.
5. McGanity, W. J., McHenry, E. W., Van Wyck, H. B. and Watt, C. L. An effect of pyridoxine on blood urea in human subjects. *J. Biol. Chem.*, 178: 511, 1949.
6. Sprince, H., Lowy, R. S., Folsome, C. E. and Behrman, J. S. Studies in the urinary excretion of "Xanthurenic acid" in normal, non-pregnant; normal, pregnant, preeclamptic and eclamptic women. *Am. J. Obst. & Gynec.*, 62: 84, 1951.
7. Wachstein, M. and Guaditis, A. Disturbance of vitamin B_6 metabolism in pregnancy. II. The influence of various amounts of pyridoxine hydrochloride upon abnormal tryptophane load test in pregnant women. *J. Lab. & Clin. Med.*, 42: 98, 1953.
8. Wachstein, M. and Lobel, S. Abnormal tryptophene metabolites in human pregnancy and their reaction to deranged vitamin B_6 metabolism. *Proc. Soc. Exper. Biol. & Med.*, 86: 624, 1954.
9. Zortman, E. R., Borvas, A. C. and Hicks, D. J. Observations in pyridoxine metabolism in pregnancy. *Am. J. Obst. & Gynec.*, 70: 645, 1955.
10. Turner, E. R. and Reynolds, M. S. Intake and elimination of vitamin B_6 and metabolites by women. II. Pregnant women. *J. Am. Dietet A.*, 31: 1119, 1955.

11. Beaton, J. R., Vavan, M. J., Lau, H. E., McGanity, W. J., McHenry, E. W. and Watt, G. L. The levels of several metabolites in blood and urine during normal pregnancy. *Am. J. Obst. & Gynec.*, 62: 156, 1951.
12. Wachstein, M. and Graffeo, L. W. The influence of vitamin B_6 on the incidence of preeclampsia. *Obst. & Gynec.*, 8: 177, 1956.
13. Swarthout, J. F., Unglaub W. G. and Smith, R. C. Vitamin B_6, serum lipids and placental arteriolar lesions in human pregnancy: a preliminary report. *Am. J. Clin. Nutrition*, 8: 434, 1960.
14. Hunt, A. D., Jr., Stokes, J., Jr., McCrory, W. W. and Stroud, H. H. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. *Pediatrics*, 13: 140, 1954.
15. Coursin, D. B. Effects of vitamin B_6 on the central nervous activity in childhood. *Am. J. Clin. Nutrition*, 4: 354, 1956.
16. Snyderman, S. E., Holt, L. E., Carretero, R. and Jacobs, K. Pyridoxine deficiency in the human infant. *Am. J. Clin. Nutrition*, 1: 200, 1953.
17. Boxer, G. E., Pruss, M. P. and Goodhart, R. S. Pyridoxine-5 phosphoric acid in whole blood and isolated leukocytes of man and animals. *J. Nutrition*, 63: 623, 1957.
18. Shaw, S. N., Johnston, P. V. and Kummerow, F. A. Effect of pyridoxine on cholesterol metabolism. *J. Nutrition*, 72: 81, 1900.
19. Glendening, M. B., Cohen, A. M. and Page, E. W. Influence of pyridoxine on transaminase activity of human placenta, maternal and fetal blood. *Proc. Soc. Exper. Biol. & Med.*, 90: 25, 1955.
20. Bloor, W. R. The determination of cholesterol in the blood. *J. Biol. Chem.*, 24: 227, 1916.
21. Cabaud, P., Leeper, R. and Wroblewski, R. Colorimetric measurement of serum glutamic oxalacetic transaminase. *Am. J. Clin. Path.*, 26: 110, 1956.
22. Rosen, F., Lowy, R. S. and Sprince, H. A rapid assay for xanthurenic acid in urine. *Proc. Soc. Exper. Biol. & Med.*, 77: 399, 1951.
23. Wachstein, M. and Guaditis, A. Disturbance of vitamin B_6 metabolism in pregnancy. *J. Lab. & Clin. Med.*, 40: 550, 1952.
24. Hillman, R. W., Cabaud, P. G. and Schenone, R. A. The effects of pyridoxine supplements on the dental caries experience of pregnant women. *Am. J. Clin. Nutrition*, 10: 512, 1962.
25. Meites, J., Feng, Y. S. L. and Wilwerth, A M. Studies of cortisone-vitamin interactions. In: Proceedings of the 92nd Annual Meeting of the American Veterinarians Medical Association, pp. 135–143, Minneapolis, 1955.