Shifts in the blood content of some materials do influence their concentration in the saliva. Further work on the utility of saliva as an indicator of nutritional status seems worthwhile.□


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## ORAL CONTRACEPTIVES AND VITAMIN $B_6$

*Women taking oral contraceptives containing estrogen show an abnormality of tryptophan metabolism, and approximately one-fourth show clear evidence of vitamin $B_6$ deficiency.*


KEY WORDS: estrogen, contraceptives, tryptophan, vitamin $B_6$, transaminase


There is as yet no perfect contraceptive, but the oral contraceptives containing estrogen are very widely used. It has been estimated that about 18.5 million women use these drugs, and it is becoming clearer that their long-term use is attended by several disorders of metabolism.[1,2]

One of the first reports of a possible effect of these drugs on vitamin $B_6$ metabolism was by D.P. Rose,[3] who showed that estrogens as well as estrogen-progestogen preparations caused increased excretion of 3-hydroxykynurenine and xanthurenic acid following a tryptophan load, and administration of pyridoxine in large doses caused the abnormal excretions of these substances to return to normal. This was taken to indicate a deficiency of vitamin $B_6$ although at that time the mechanism whereby estrogens affected tryptophan metabolism was not clear. The analogy was drawn with the situation which existed in pregnancy. It had been demonstrated several years previously that in the latter part of pregnancy women excreted larger amounts of xanthurenic acid after a tryptophan load than non-pregnant women and this was also corrected by pyridoxine.[4] This finding has been confirmed on several occasions since then. It was not clear from these studies whether the demands of the fetus induced the vitamin $B_6$ deficiency or whether the altered hormonal state of pregnancy was associated with the metabolic abnormality. The studies of Rose might support the latter. Rose's original study was quickly confirmed by J.M. Price, M.J. Thornton, and L.M. Mueller,[5] who also showed that when a tryptophan load was given to women taking an oral contraceptive the urinary excretion of several other metabolites of tryptophan besides xanthurenic acid was higher than in women who were not taking such drugs.

In a more recent study,[6] Rose and co-workers have investigated in more detail tryptophan metabolism in women on oral contraceptives. In a preliminary study they characterized the metabolic response to a tryptophan load in a healthy male on a vitamin $B_6$-deficient diet for 20 days. They measured excretion of xanthurenic acid, kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and 4-pyridoxic acid. They also measured the pyridoxal-dependent enzymes alanine aminotransferase and aspartate aminotransferase in erythrocytes, plus the stimulatory effect on these enzymes of pyridoxal phosphate in vitro.

The enzyme tryptophan pyrrolase catabolizes tryptophan to formyl-kynurenine, from which kynurenine is formed. Kynurenine is then hydroxylated to 3-hydroxykynurenine. Kynurenine and 3-hydroxykynurenine are converted to kynurenic acid and xanthurenic acid (XA) respectively by pyridoxal phosphate-dependent transaminases. 3-Hydroxykynurenine can also be converted to 3-hydroxyanthranilic acid by another pyridoxal phosphate-dependent enzyme, kynureninase. An increase in the ratio of 3-hydroxykynurenine to 3-hydroxyanthranilic acid (HK/HA) is consid-

ered to be another good indicator of vitamin $B_6$ deficiency. 4-Pyridoxic acid (4-P) is the excretion product of pyridoxine.

In the preliminary study, Rose et al. found predictably that XA and kynurenine rose while 4-P fell and the ratio HA/HK rose, more because of increased HK excretion. Erythrocyte alanine aminotransferase activity fell, but there was no change in aspartate aminotransferase.

Thirty-one women who had been taking a variety of contraceptives containing estrogen for periods of six to 36 months were next compared with 22 controls. There was a significantly higher excretion of the tryptophan metabolites, and a significantly greater HK/HA ratio, but the mean excretion of 4-P was unchanged. However, seven of the women taking contraceptives had subnormal 4-P excretions and there was a strong negative correlation between the HK/HA ratio and 4-P excretion. Of these seven women, six had elevated HK/HA ratios. The basal aspartate aminotransferase activity was surprisingly higher in women on contraceptives for longer than six months. The significance of this is not clear. Three women who had this clear evidence of vitamin $B_6$ deficiency as shown by decreased 4-P excretion, elevated HK/HA ratios, and reduced erythrocyte alanine aminotransferase activity were given 20 mg. pyridoxine-HCl daily for one month, and this resulted in complete reversal of all the abnormalities. The data thus reinforce previous experiments and prove conclusively that contraceptives affect tryptophan metabolism, and in approximately one-fourth of the cases cause vitamin $B_6$ deficiency.

To explain the uniform occurrence of the abnormality of tryptophan metabolism even in those women with normal 4-P excretion, the authors propose that the derivatives of the estrogen may specifically inhibit one of the enzymes of the tryptophan pathway, kynureninase, and that this leads to an increase in excretion of metabolites proximal to this step—hence the increased HK/HA ratios. Another possibility considered is that the estrogens activate metabolism of tryptophan plus causing a block in degradation of the tryptophan metabolites. It has already been shown, in many etiologically dissimilar human diseases, that increased activity of tryptophan pyrrolase, rather than vitamin $B_6$ deficiency, is the cause of the increased excretion of the metabolites of tryptophan.[7]

It is unfortunate that in none of these studies is any mention made of the possible clinical implications of the results. The clinical expressions of vitamin $B_6$ deficiency are well known, and the dermatological manifestations especially should be easily recognized, although the central nervous system changes, such as lethargy and irritability, may go unnoticed. It is not known whether a systematic study of patients taking oral contraceptives has shown a significant incidence of any symptoms or signs of vitamin $B_6$ deficiency. The authors do not give any details of the nutritional state of these women who were vitamin $B_6$ deficient, and it would have been of some importance to know whether their dietary intake of the vitamin was possibly suboptimal. Recently attention has been directed to another aspect of vitamin $B_6$ deficiency, i.e. increased formation of urinary calculi,[8] and this might well warrant study in women on oral contraceptives. Although in more affluent countries the diet will supply adequate amounts of vitamin $B_6$, in those parts of the world where there is already clinical and laboratory evidence of vitamin $B_6$ deficiency, the use of oral contraceptives could possibly lead to a worsening of the deficiency state. This will obviously require future study. □


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