Oral contraceptives: effects on folate and vitamin B_{12} metabolism

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Women who use oral contraceptives have impaired folate metabolism as shown by slightly but significantly lower levels of folate in the serum and the erythrocytes and an increased urinary excretion of formiminoglutamic acid. The vitamin B_{12} level in their serum is also significantly lower than that of control groups. However, there is no evidence of tissue depletion of vitamin B_{12} associated with the use of oral contraceptives. The causes and clinical significance of the impairment of folate and vitamin B_{12} metabolism in these women is discussed in this review of the literature. Clinicians are advised to ensure that women who stop taking "the Pill" because they wish to conceive have adequate folate stores before becoming pregnant.

Les femmes qui emploient les contraceptifs oraux ont une altération du métabolisme de l'acide folique comme le montre la baisse faible mais significative des taux d'acide folique dans le sérum et les érythrocytes, et l'augmentation de l'excrétion urinaire de l'acide formiminoglutamique. Les concentrations sériques en vitamine B_{12} sont aussi significativement plus basses que chez les groupes témoins. Toutefois, il n'y a pas de preuve d'une déplétion tissulaire en vitamine B_{12} reliée à l'utilisation des contraceptifs oraux. Les causes et la signification clinique de l'altération du métabolisme de l'acide folique et de la vitamine B_{12} chez ces femmes sont commentées dans cette revue de la littérature. On conseille aux cliniciens de s'assurer que les femmes qui interrompent "la pilule" parce qu'elles souhaitent concevoir possèdent des réserves adéquates d'acide folique avant de devenir enceinte.

There is evidence that oral contraceptives interfere with and impair the body's metabolism of folic acid, or folate, and vitamin B_{12}. However, several reviewers[1-5] have cited results that negate this evidence, creating some confusion and controversy. This may have led some physicians to incorrect diagnosis and management of their patients. I shall review the available data on this topic, discussing both the established and the controversial effects of "the Pill" on folate and vitamin B_{12} metabolism, and describing the clinical significance of impairment of the metabolism of these substances in users of these compounds.

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Oral contraceptives and folate metabolism

Effect of oral contraceptives on serum folate level

In a preliminary report in 1968 I and my colleagues[6] noted that a group of women using "the Pill" had a significantly lower mean serum level of folate than a control group. In a later, more detailed study we found that a group of oral contraceptive users had a lower mean serum level of folate and a higher percentage of subnormal folate levels than a control group.[7,8] We also observed that the mean serum level of folate in the group using oral contraceptives decreased with increasing duration of use of these compounds, and that the folate level returned to normal within 3 months after the women stopped using the Pill.[8] Following the publication of our preliminary report in 1968, our results became controversial when five separate groups[9-13] reported that they had not demonstrated any statistically significant difference between the serum levels of folate in users of the Pill and in nonusers. The subject is still considered controversial by many despite at least 12 reports[6-8,14-24] that confirmed our original findings. Other studies[9-13,25-30] reported no statistically significant difference between the serum levels of folate in users and nonusers of the Pill.

Effect of oral contraceptives on erythrocyte folate level

In our 1971 report[8] we noted that the mean level of folate in the erythrocytes of the group using oral contraceptives was significantly lower than that of the control group, and that there was a significant rise in the erythrocyte level of folate within 3 months in women who stopped taking these compounds. A number of studies[8,14,16,18-20,23,31-33] have reported that the mean level of folate in the erythrocytes, based on the findings of microbiologic assays, in groups taking the Pill was significantly lower than that of control groups. Three studies[9,27,30] have failed to show any statistically significant differences between such groups.

Effect of oral contraceptives on urinary excretion of formiminoglutamic acid (FIGLU)

FIGLU is an intermediary product of the metabolism of histidine that requires the reduced form of folic acid to be further metabolized. Patients with a folate deficiency, when given a test dose of histidine, show an increase in the amount of FIGLU excreted in the urine.[34] We found that women using oral contraceptives excreted significantly more FIGLU in the urine after a histidine load than controls, and that the levels of FIGLU in the urine decreased to normal within 2 to 4 months after the use of these compounds was

stopped.[7,8] The higher level of FIGLU excreted by oral contraceptive users was noted by two other groups of investigators.[14,18] Since FIGLU excretion tends to increase in early pregnancy,[35] it is not clear whether the increases in women using oral contraceptives are due to a folate deficiency associated with the use of these compounds or to another effect that mimics early pregnancy.

Oral contraceptives and megaloblastic anemia

Several cases of megaloblastic anemia related to a folate deficiency and attributed to or associated with the use of the Pill have been reported.[36-54] In some of these cases there were associated contributory factors, such as a mild malabsorption syndrome or a dietary folate deficiency, and it is not clear whether megaloblastic anemia would have occurred as the result of using the Pill in the absence of these other factors. Megaloblastic changes in the cervicovaginal cells of oral contraceptive users were noted by Whitehead and colleagues.[55] These changes were found even in those with normal serum levels of folate but could be corrected with folate therapy and were attributed to the local effect of the Pill on the folate metabolism of the target organ.[55,56] In contrast, Ross and associates[28] found no more megaloblastic changes in the cervical tissue of those who used than in those who did not use oral contraceptives.

Effect of oral contraceptives on hemoglobin level, hematocrit and erythrocyte indices

In general, no significant effect of oral contraceptives on hemoglobin levels or the hematocrit has been reported. Groups using these compounds are reported to have equal or slightly higher mean hemoglobin and hematocrit levels than control groups.[8,13,18,20,21,23,24,28] These slightly higher levels are probably related to the smaller menstrual blood loss that is characteristic of oral contraceptive users. Fisch and Freedman[57] reported that erythrocyte indices in oral contraceptive users, adjusted for age and menstrual blood loss, were slightly but significantly raised, whereas hemoglobin and hematocrit levels and the erythrocyte count were decreased. The slight increase in the mean corpuscular volume of users of the Pill has also been reported by others.[13,23,24,58]

Impaired folate metabolism in oral contraceptive users

Pathogenesis: Experiments in animals have shown a close metabolic relation between the presence of sex steroids and changes in folate coenzymes in the liver and other target organs.[59-70] However, the mechanism of the impairment of folate metabolism both in experimental animals and in humans remains unclear. Initially the reports that the Pill inhibited the effect of folate conjugase[71] and caused malabsorption of folate polyglutamates[39,72] seemed to have provided a satisfying explanation, but two subsequent reports[25,48] failed to show any malabsorption of folate polyglutamates in oral contraceptive users or any inhibitory effect of these compounds on folate conjugase.[25] We subsequently found that women using the Pill excreted more folate in their urine than nonusers.[73] This increased excretion of folates in the urine, which was also reported in rats treated with oral contraceptives[62,70] and in pregnant women,[74] may in part explain the lower levels of folate in the serum and erythrocytes of oral contraceptive users. Two other mechanisms have been proposed for the impairment of folate metabolism in association with the use of oral contraceptives. One is based on the role of folate binders, whose level is reported to be increased in the serum[31,75] and in the leukocytes[75] of users of the Pill. It is postulated that these substances, which tightly bind dihydro-, tetrahydro- and formyltetrahydrofolates, may make folates unavailable to the cells and thus cause folate deficiency at the cellular level.[56,75] As well, Maxwell and coworkers[76] stated that oral contraceptives may cause folate depletion by accelerating the metabolism of folates through the induction of microsomal enzymes that require folic acid. Oral contraceptives were found to be active inducers of liver microsomal enzymes in mice and rats but not in guinea pigs.[69]

Clinical significance: Many of the studies I have cited indicate that oral contraceptives impair folate metabolism and produce some degree of folate depletion. However, this effect is mild and unlikely to cause anemia or megaloblastic changes in women who have a good dietary intake of folate and can absorb it properly. Consequently, when a folate deficiency is associated with megaloblastic changes it should not be attributed to the use of the Pill alone; additional contributory factors, such as poor dietary intake of folate or silent malabsorption, should be looked for. Since pregnant women are predisposed to the development of a folate deficiency[35] and thus to complications associated with this deficiency, we were concerned that women who became pregnant shortly after stopping the use of oral contraceptives might be at a higher risk of these complications.[8] Martinez and Roe[22] demonstrated that this concern was valid and that women who became pregnant within 6 months after discontinuing oral contraceptives had lower levels of serum and erythrocyte folate than those who had not used these compounds. It is reasonable to ensure that a woman who stops using the Pill and contemplates pregnancy either has adequate folate stores or takes folate supplements before becoming pregnant.

Oral contraceptives and vitamin B_{12} metabolism

Effect of oral contraceptives on serum and erythrocyte levels of vitamin B_{12} and on urinary excretion of methylmalonic acid

There is general agreement that serum levels of vitamin B_{12} are lower in users of the Pill than in nonusers,[15,16,19,20,24,29,31,77-81] whether the level is determined by microbiologic[12,24,31,77-79] or radioisotope[15,24,29,81] assay. However, evidence of vitamin B_{12} depletion elsewhere in the body is lacking. Thus, Wertalik and collaborators[15] reported that despite the lower level of vitamin B_{12} in the serum of oral contraceptive users, the erythrocyte levels of vitamin B_{12} were similar in these women and in controls, and we found no significant difference between the urinary excretion of methylmalonic acid in users and in controls.[24] As well, we found no significant difference

in the urinary excretion of this acid between oral contraceptive users whose serum levels of vitamin B_{12} were low and those whose levels were normal.[24]

Effect of oral contraceptives on vitamin B_{12} binders

Bianchine and colleagues[82] originally reported that women using oral contraceptives had a higher unsaturated vitamin B_{12} binding capacity in their serum than did control subjects. However, subsequent studies[15,24,80,81] have failed to show any significant difference in this measure between oral contraceptive users and nonusers. We also found no such difference, although we did note that the total vitamin B_{12} binding capacity of the serum as well as the transcobalamin I levels were significantly lower in users of the Pill than in nonusers.[24] Costanzi and associates,[81] however, found no significant difference in the total serum level of transcobalamin I between users and nonusers of the Pill.

Low serum levels of vitamin B_{12} in oral contraceptive users

Pathogenesis: Since the absorption and the urinary excretion of vitamin B_{12} in oral contraceptive users are normal[15,24,80] and their lower serum levels of vitamin B_{12} are not associated with evidence of tissue depletion of this substance, our findings of lower total vitamin B_{12} binding capacity[24] and lower transcobalamin I levels in the serum of the users could explain their low serum levels[24] of this vitamin. Although there is a close interrelation between folate and vitamin B_{12} metabolism, the mechanism that causes low serum levels of vitamin B_{12} in those using the Pill seems to be different from the one that causes low serum levels of folate as there is no correlation between the levels of those substances,[15,24] and folate therapy does not correct the low serum levels of vitamin B_{12} in oral contraceptive users.[15] However, there may be some relation between the low serum levels of vitamin B_{12} in oral contraceptive users and impaired tryptophan or pyridoxine metabolism. Boots and coworkers[83] demonstrated that baboons treated with oral contraceptives had lower serum levels of vitamin B_{12} than control animals but that the lowering of the serum vitamin B_{12} levels in the treated group could be prevented with pyridoxine therapy. Briggs and Briggs[79] reported that the low serum vitamin B_{12} levels of oral contraceptive users could be corrected with a supplementary multivitamin preparation (Surbex 500) that provided 5 mg of pyridoxine and 4 μg of cyanocobalamin (vitamin B_{12}) a day. It was not clear whether the correction was due to the pyridoxine or the vitamin B_{12}.

Clinical significance: Although the serum levels of vitamin B_{12} may be lowered to subnormal values in those using the Pill this is not associated with evidence of tissue depletion of vitamin B_{12} and has no clinical significance as long as the physician is aware of this effect of oral contraceptives. However, since pernicious anemia may also occur in women of reproductive age, the low serum vitamin B_{12} level of a woman who is taking oral contraceptives should not be disregarded. The clinician may either suggest that the patient temporarily stop taking the Pill to see if the serum level of vitamin B_{12} increases or perform a Schilling test to exclude the possibility that the problem is caused by vitamin B_{12} malabsorption.

Discussion

Oral contraceptives impair folate metabolism and tend to reduce the serum and erythrocyte levels of folate and to increase the urinary FIGLU excretion. The effect is very mild and by itself should not cause a clinically significant folate deficiency unless there are associated contributory factors. Consequently, megaloblastic anemia due to folate deficiency should not be attributed to the use of oral contraceptives only; additional factors, such as decreased intake or absorption, or increased need for or loss of folate should be looked for. Similarly, oral contraceptives may produce a low serum level of vitamin B_{12}. However, this low level is not associated with a true deficiency of the vitamin and is most likely due to the changes in the serum vitamin B_{12} binders.

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