Hormone replacement therapy and cobalamin status in elderly women

Ralph Carmel, Jeanne M Howard, Ralph Green, Donald W Jacobsen, and Colleen Azen

ABSTRACT Serum cobalamin concentrations are frequently low in the elderly but the cause is often not apparent. Because oral contraceptives have been associated with low cobalamin concentrations in young women, we compared hormone use with cobalamin status in elderly women to determine whether it could account for their unexplained low cobalamin concentrations. Thirty-eight of the 111 women had abnormal cobalamin status (defined by low cobalamin, elevated methylmalonic acid, and/or elevated homocysteine concentrations) and 73 had normal status. There was no difference in hormone use between the two groups: 7 (18.4%) of the 38 cobalamin-deficient subjects used estrogens compared with 20 (27.4%) of the 73 control subjects. No differences in hormone use were apparent either when analysis was confined to abnormal serum cobalamin concentrations alone. Similarly, the 27 women taking hormones and the 84 women not taking hormones did not have significantly different serum cobalamin or serum total homocysteine concentrations. Indeed, hormone users had slightly, though not significantly, higher cobalamin concentrations and lower homocysteine concentrations than nonusers; furthermore, hormone users also had significantly lower serum methylmalonic acid concentrations. Thus, neither cobalamin concentrations nor cobalamin metabolic status were significantly worse in elderly women taking estrogen than in those not taking it (and, if anything, may have been slightly better). Hormone use does not appear to be a significant contributor to the low cobalamin concentrations or the mild metabolic evidence of cobalamin deficiency so often seen in the elderly. Am J Clin Nutr 1996;64:856–9.

KEY WORDS Cobalamin, aging, homocysteine, methylmalonic acid, estrogen

INTRODUCTION

Oral contraceptive use may cause low cobalamin concentrations in young women (1–9). Whether hormone replacement therapy, which is widely used in elderly women (10), does the same is unknown. If it does, then hormone use might explain at least some of the low serum cobalamin concentrations seen frequently in the elderly.

This question is of concern for several reasons. Cobalamin concentrations are low in 6–18.3% (11, 12) of elderly people, suggesting that millions of older Americans may be affected. Although megaloblastic anemia is rare, metabolic studies have shown that many low cobalamin concentrations that seem clinically innocent represent unequivocal, albeit usually mild, deficiency of the vitamin (13–17). The cause of most of the low concentrations has resisted identification, however. Only a few are attributable to pernicious anemia (lack of intrinsic factor) (18) and less than one-half of the remainder are associated with malabsorption of food cobalamin (16, 19, 20).

An important gap remaining in understanding the common problem of low cobalamin concentrations in the elderly is to identify the cause in the many subjects in whom it remains unexplained. Therefore, we studied 111 elderly women whose cobalamin status had been defined by serum cobalamin concentrations as well as by metabolite concentrations and assessed whether hormone use was associated with cobalamin-related abnormalities.

PATIENTS AND METHODS

Use of hormone replacement therapy was assessed in 38 women who had been found to have abnormal cobalamin status during a study of cobalamin status in free-living elderly people aged ≥ 60 y at adult education centers, social clubs, and a Department of Veterans Affairs outpatient clinic (where both employees and patients were studied). Abnormal status was identified by one or more of the following findings in the absence of any other explanation: a low serum cobalamin concentration (9 women), an elevated serum methylmalonic acid concentration (11 women), or an elevated serum total homocysteine concentration (23 women); 5 of the women had more than one abnormality. Whereas other disorders can also cause homocysteine elevation (21), the most common of these, folate deficiency, was excluded in all cases by serum folate assay; the only woman with a low folate concentration in this group also had a low cobalamin concentration.

These 38 women represented, with certain exclusions, the entire female cohort found to have cobalamin-related abnormalities at the three testing sites, where 729 subjects of both sexes had been screened. In collecting this relatively large

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number of 38 affected women for analysis of hormone use, we excluded certain types of subjects: five women because perni-
cious anemia or malabsorption of food cobalamin explained their low cobalamin concentrations; 14 women either because they had been taking cobalamin supplements at the time of testing or because they had renal insufficiency, which could have artifactually affected their methylmalonic acid and/or homocysteine concentrations; and six women because they were unavailable for interview. No other selection factors were applied.

Seventy-three concurrently studied subjects, whose tests of cobalamin status had given normal results, were included as control subjects from the same survey of cobalamin status. Fourteen other control subjects were excluded because they had been taking cobalamin supplements at the time of testing or because of renal insufficiency, and 22 subjects were excluded because they were unavailable for interview. Other than these exclusions, no conscious selection factors were applied. The study was approved by the Institutional Review Board.

All 111 women were questioned in detail about their use of hormones at the time of their blood sampling. Twenty-seven women were found to be taking estrogens: 16 took Premarin (conjugated estrogens; Wyeth-Ayerst, Philadelphia) alone or in combination with another hormone, such as medroxyprogesterone, whereas the rest took other estrogen preparations. All but four women had been taking their hormones for > 1 y; the four exceptions were women who took hormones for 1–9 mo. The assays of serum cobalamin (22) and total homocysteine (23) concentrations had been performed as described previously. Serum methylmalonic acid was measured by stable-isotope dilution and gas chromatography–mass spectrometry using the method of Rasmussen (24), except that 5 nmol rather than 1 nmol (CD3)2methylmalonic acid was used as the internal standard. The 111 subjects underwent all three blood tests, except for 3 women in whom methylmalonic acid concentrations were not determined and for 1 woman in whom homocysteine was not assayed. None of the 111 women in this study had macrocytic anemia or any other clinical evidence of cobalamin deficiency.

All variables exhibited a positive skew, which was normalized by a log transformation. Statistical analysis was done with Student’s t test on log-transformed values for continuous data. Fisher’s exact test was used for dichotomous forms of the variables. Two-tailed P values < 0.05 were considered significant. SAS (25) statistical software was used.

RESULTS

The ages of the 38 women with abnormal cobalamin status and the 73 women with normal status were similar (x ± SD: 74 ± 7 y compared with 73 ± 6 y). Seven of the 38 women with abnormal cobalamin status (18.4%) were found to be taking hormones at the time that their cobalamin status had been analyzed, compared with 20 of the 73 women with normal cobalamin status (27.4%). This difference was not significant (P = 0.36 by Fisher’s exact test); if anything, hormone use was less frequent than more frequent in women with abnormal cobalamin status.

Expressed in another way, abnormal cobalamin status was not more prevalent in hormone users (7 of 27 women, 25.9%) than in nonusers (31 of 84 women, 36.9%); this too was, if anything, slightly but not significantly less frequent among hormone users. The findings were similar when analysis was confined to serum cobalamin concentrations, without the metabolic data related to cobalamin status. Three of 27 (11.1%) women using estrogens had low cobalamin concentrations compared with six of 84 (7.1%) women not taking hormones (P = 0.69 by Fisher’s exact test).

Serum cobalamin concentrations were not significantly lower in hormone users; indeed they were slightly but not significantly higher than in nonusers (Table 1). Methylmalonic acid concentrations were significantly lower in the women taking hormones; in other words, methylmalonic acid concentrations too were even less indicative of cobalamin deficiency in women taking hormones than in control subjects.

Because the 27 women taking estrogens were younger than the 84 not using hormones (71 ± 5 y compared with 74 ± 7 y) and the oldest hormone user was 79 y old, we repeated all analyses after excluding the 17 nonusers who were ≥ 80 y old. The ages of the groups were now virtually identical (71 ± 5 y for each group). None of the previously mentioned outcomes were altered in any way as a result. Results also remained unchanged after the four women taking hormones for < 1 y were excluded from analysis, one of whom had a low cobalamin concentration.

DISCUSSION

Most observers suggest that oral contraceptives depress serum cobalamin concentrations slightly (1–9). This putative effect of contraceptives is only infrequently accompanied by megaloblastic anemia, and cobalamin absorption as measured by the Schilling test is always normal (1, 2, 6). The reason for this phenomenon is unknown.

Information is not available about any effect of hormone replacement on cobalamin status in the elderly. A study of menopausal women with a mean age of 50.6 y who took estrogen reported no decrease in cobalamin concentrations compared with control subjects but suggested that the incidence of subnormal concentrations might have been increased slightly (8).

We addressed this issue because cobalamin concentrations are often low in the elderly (11, 12, 26–29) and metabolic abnormalities suggestive of mild cobalamin deficiency are

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| Comparison of cobalamin-related data in elderly women taking hormones and in control subjects
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<th>Women using hormones</th>
<th>Women not using hormones</th>
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<tbody>
<tr>
<td>Serum cobalamin (pmol/L)</td>
<td>266 (131, 497) [27]</td>
<td>258 (151, 534) [84]</td>
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<tr>
<td>Serum methylmalonic acid (nmol/L)</td>
<td>213 (150, 313) [26]</td>
<td>252 (170, 394) [82]</td>
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<tr>
<td>Serum total homocysteine (μmol/L)</td>
<td>13.0 (9.0, 19.4) [27]</td>
<td>13.6 (9.0, 20.2) [83]</td>
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1 Data are geometric means; 10th and 90th percentiles are in parentheses and n values are in brackets. Normal values are 140–750 pmol/L for cobalamin, 79–376 nmol/L for methylmalonic acid, and 4.0–17.5 μmol/L for homocysteine.

2 Significantly different from women using hormones, P = 0.03.
even more common (30), yet the reason for this phenomenon is often not apparent. Pernicious anemia and other classical malabsorptive states are only infrequently implicated (18), and even the more common entity of malabsorption of food cobalamin occurs in less than one-half of such patients with low cobalamin concentrations (16, 19, 20).

Thus, other causes having nothing to do with diminished absorption must be sought to explain most low cobalamin concentrations in the elderly. Dietary inadequacy of cobalamin does not appear to be a factor (29, 31), nor does increased urinary excretion of the vitamin (32).

The findings reported here appear to exclude hormone replacement therapy as a significant cause of the frequently low cobalamin concentrations in the elderly. The lack of effect of estrogen on cobalamin status in the elderly differs from the findings in young women using oral contraceptives.

The explanation for this difference is not readily apparent. A type II error of a false-negative result due to small sample size cannot be dismissed completely, but seems unlikely. The mean cobalamin concentrations in our study were, if anything, slightly (but not significantly) higher rather than lower in the women using hormones than in the control subjects; similarly, serum metabolite concentrations tended to be less abnormal in the women using hormones and, indeed, methylmalonic acid concentrations were significantly lower in them. The lack of even a nonsignificant trend in favor of a hormone effect speaks against a type II error. Moreover, we studied more subjects than did many of the studies that had defined a significant effect of oral contraceptives in young women. Finally, our findings agree with those in a younger group of menopausal women (8) in suggesting that the absence in the elderly of the effect seen with oral contraceptive use by young women is real. It remains to be established whether this dichotomy between the effects of hormone use in the elderly and oral contraceptive use reflects differences in cobalamin metabolism as people age, differences attributable to types of hormone preparations and doses, or other factors.

As mentioned, our metabolite data also suggest that serum cobalamin concentrations as well as serum concentrations of methylmalonic acid and homocysteine, whose elevation is often a sensitive marker of cobalamin deficiency (21, 33), were not worsened in elderly women using hormones. Previous studies of the effect of oral contraceptive use on homocysteine concentrations have not established any clear pattern (9, 34). Homocysteine is of potential importance because of the associations between elevated concentrations and vascular disease (34, 35). The effect of hormone use on methylmalonic acid has not been studied to our knowledge. The explanation for the surprisingly and significantly lower methylmalonic acid concentrations in hormone users (P = 0.03) is not readily apparent.

Although it was not the purpose of this study, it is worth noting in passing that serum folate concentrations were not decreased in elderly women using hormones either (data not shown). Only three women, one hormone user and two nonusers, had subnormal serum folate values. As with cobalamin concentrations, this lack of effect differs from the possible folate-lowering effect of oral contraceptives described in younger women (5, 36, 37). However, our folate results must be interpreted cautiously because folate supplement use, unlike cobalamin supplement use, was not an exclusionary factor in the study.

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REFERENCES


