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THE EFFECT OF ORAL CONTRACEPTIVES ON BLOOD VITAMIN A LEVELS AND THE ROLE OF SEX HORMONES

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Oral contraceptives elevate blood vitamin A levels. The estrogen component of the contraceptive formulation seems to be responsible for this phenomenon by increasing levels of retinol-binding protein.

Key Words: oral contraceptives, vitamin A levels, carotenoid levels, sex hormones, retinol-binding protein levels, prealbumin.

Blood vitamin A levels are generally used to assess vitamin A status. These levels, however, can be affected by the use of oral contraceptives (OC).[1-8] In 1971, Gal et al.,[1] investigates the effect of using OC on human plasma vitamin A levels. They compared two groups of healthy women aged 20 to 32. One group was composed of 20 women with a regular menstrual cycle and the other of 22 women taking various chemical forms of OC for at least three months. Vitamin A and carotenoids levels were measured at three to five and at 18 to 21 days of the menstrual cycle. Plasma vitamin A levels were significantly higher, at both times of measurements, in the group taking the pill. In contrast, carotenoid levels were depressed, although this difference was significant only at 18 to 21 days of the cycle. They concluded that exogenous esteroids have a profound influence on vitamin A metabolism. This observation was re-examined by Yeung[2] in human subjects and in rats. He first compared two groups of healthy college women between the ages of 20 to 23 years. One group consisted of 11 women with regular menstrual cycles who had never taken OC. The other was formed by 11 women who had been using OC for various lengths of time. Vitamin A and carotene levels were measured several times during the menstrual cycle. Their body temperature also was recorded daily. It was found in this study that plasma vitamin A levels of OC users was significantly higher than in non-users for each one of the evaluations during the menstrual cycle. The differences in carotene levels were not significant, except at one to five days of the cycle in the OC users. Furthermore, the change in vitamin A levels was not related to changes in body temperature. In the parallel study of rats, three groups weighing an average of 170 g were compared. Group one was "control", group two was "treatment control" to which saline solutions were given and group three was the "experimental group". This latter group received a commercial contraceptive formulation daily for 28 days at a level proportional by weight to that consumed by a reference woman (55 kg). Unlike human subjects, rats given OC at this dose failed to show higher plasma vitamin A levels than controls. The liver vitamin A reserves, however, were lower in the OC-treated animals. More important, the mean liver depletion rate of vitamin A as well as its utilization was significantly greater in the rats given OC. This study confirmed the observations of Gal et al.[1] and suggested that the use of OC may impose greater vitamin A requirements.

These early observations about the experimental effect of OC on plasma vitamin A levels were supported epidemiologically by Smith et al.[3] and Prasad et al.[4] who again found that OC users have higher plasma vitamin A levels than non-users.

At this point, however, the component of OC and the mechanism by which OC promoted this elevation in plasma vitamin A was unknown. Nevertheless, the regular cyclic pattern of vitamin A concentration in blood during the menstrual cycle suggested an association be-

tween changes in sex hormones and changes in vitamin A levels.[9] Thus, Yeung and Chan[5] examined whether the rise in plasma vitamin A was due to the estrogen or to the progestogen component of the pill. In this study, female students were given, after a control period, two different commercial OC. One contained the progestogen norethindrone as its sole ingredient; the other contained the estrogen, mestranol from Day 5 to 18 of the cycle and both mestranol and norethindrone from Day 19 to 26. Plasma vitamin A levels of subjects receiving the pill containing the estrogen, however, experienced a significant elevation in plasma vitamin A. Neither of the two compounds showed an effect on carotene levels. It was concluded that the elevated levels of vitamin A observed in women taking OC are due to the estrogen content in the steroid preparation.

As regards the mechanism of this phenomenon, the work of Supopark and Olson[6] suggested that the elevation in vitamin A levels was due to a higher circulating level of retinol-binding protein (RBP). In their experiments, a combination type estrogen-progestogen preparation was given to rats at a level 50 times greater than the normal human dose. They found that retinol in serum of OC-treated rats was associated entirely with a protein fraction with the characteristics of RBP. Supporting this observation, Michaelsson et al.[7] also found significantly higher levels of RBP in women taking OC than in non-users.

More recently, Vahlquist et al.[8] have studied the role of sex hormones on the levels of vitamin A transporting proteins in humans. In one experiment, they measured the levels of prealbumin, RBP, estradiol and progesterone daily in the blood of four women during a normal ovulatory cycle. Prealbumin showed no consistent pattern of variation during the menstrual cycle. RBP levels, however, decreased significantly shortly before the preovulatory estradiol peak. Furthermore, there seemed to be two RBP maxima during the menstrual cycle, one before and the other after ovulation. It is suggested by the authors that the post-ovulatory RBP maximum is induced by the appearance of the sharp mid-cycle estradiol peak and that the pre-ovulatory RBP maximum is the result of the second estradiol peak of the preceding menstrual cycle. The depression of RBP levels in the mid-cycle is believed to be the lack of estradiol stimulus. It is unfortunate that vitamin A levels were not measured in this particular experiment, since the peaks in RBP levels observed in this study do not exactly correspond to the vitamin A peaks observed by the other investigators.[9]

In a subsequent experiment, three of these women were given OC treatment, first a formulation containing 50 μg of the synthetic estrogen ethinyl estradiol and later a formulation containing 4 mg of estradiol and 2 mg of estriol. Both formulations contained norethisterone acetate as the gestagen component. Both treatments induced a significant elevation in RBP levels during the period studied. The relative effect of each of these treatments in raising RBP levels, however, cannot be evaluated in this study because of the different levels of exogenous hormonal treatment used. It is also demonstrated that administration of ethinyl estradiol suppresses the endogenous estradiol peak and induces a slow increase in the prealbumin level that follows the rapid increase of RBP by several days. Finally, it was shown that OC treatment significantly elevated vitamin A levels. Furthermore, the relative increase of plasma vitamin A correlated significantly ($r=0.92$) with the increase of RBP levels. The prealbumin level, however, showed a less significant relationship with plasma vitamin A. It is concluded that an increase in RBP levels accounts for the raised serum vitamin A during OC treatment in humans. Furthermore, it was suggested that the estrogen component of the treatment was responsible for the observed changes.

In general, it is clear that OC treatment elevates blood vitamin A levels. Carotenes, however, are not significantly affected. Furthermore, under normal conditions, there seems to be no danger of vitamin A toxicity due to the use of OC, since the induced change in vitamin A levels still falls within the normal range and is accompanied by a corresponding change in RBP. The observed increments have been of approximately 50 percent in the rat and 35 percent in humans.[5,8]

Estrogen appears to be responsible for the enhancement of RBP levels that brings about

a concomitant increase in blood vitamin A concentration. Some interesting questions, however, remained to be answered. Do the elevated RBP levels found upon OC treatment result from an increase in RBP synthesis, an increased release of preformed RBP from the liver or to a reduction in RBP turnover? These studies will be awaited with interest.

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