FERTILITY AND STERILITY
Vol. 35, No. 4, April 1981
Printed in U.S.A.
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ELEVATED PROLACTIN LEVELS IN ORAL CONTRACEPTIVE PILL-RELATED HYPERTENSION*

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Twenty women whose blood pressure became elevated during oral contraceptive treatment had higher serum prolactin levels (31 ± 5.3 μg/liter) than did 20 normotensive pill takers (16.1 ± 1.8 μg/liter) and 20 women who were not taking the pill (14 ± 1.1 μg/liter), and the higher level was maintained (30 ± 3.5 μg/liter) after the pill was discontinued and blood pressure had become normal. This increase in prolactin levels was not related to differences in age or mode of treatment, and it is thought to reflect an alteration in dopaminergic transmission in patients with pill-related hypertension. Fertil Steril 35:403, 1981

Hypertension occurs in some 5% of women taking oral contraceptives.[1] It may be related to stimulation of the renin-aldosterone-angiotensin system,[2-4] but biochemical changes are also seen in women taking the pill who have normal blood pressure.[5] Animal experiments indicate that dopamine may play a part in the regulation of blood pressure, since L-dopa, a dopamine precursor, and apomorphine, a dopamine agonist, decrease blood pressure in the rat and the cat.[6, 7] As serum prolactin levels also reflect changes in the transmission of dopamine, we have examined prolactin levels in women with pill-associated hypertension and have shown that the levels are higher than those in normotensive pill users.

Received September 22, 1980; accepted December 12, 1980.
*Supported by grants from the Foundation of Gynecological Research, Finland, the Finnish Cultural Foundation (P. L. and T. R.), the Research Council for Medical Sciences, Academy of Finland, and the Medical Research Council of England (M. S.).
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SUBJECTS AND METHODS

Twenty women who developed hypertension (sitting blood pressure higher than 140/90 mm Hg, two or three determinations for each patient) while taking the pill and 20 normotensive pill users were studied. All subjects used combined agents for contraception, usually 30 μg of ethinylestradiol and 150 μg of levonorgestrel. The groups were similar in age (29.5 ± 1.5 and 25.8 ± 1.1 years). All had normal cycles and all were normotensive when the pill was started and had taken the pill for at least 3 months (35 ± 7.4 months in the hypertensive group; 29 ± 5.8 months in the normotensive group). Serum samples were obtained from both groups between 3 P.M. and 6 P.M. on the day after clinical examination.

In the hypertensive group, the pill was discontinued at the end of the current cycle, and another serum sample was taken at the end of the following nontreatment cycle. Samples were also collected from 20 apparently healthy women (age 26.5 ± 1.3 years) who were not on the pill. All samples were stored at −20° C until assayed.

TABLE 1. *Serum Prolactin Concentrations in Women during and after Oral Contraception and in Women Not Taking the Pill*

Subjects	No. of subjects	Serum prolactin[a]
		μg/liter
Hypertensive pill users		
While taking the pill	20	31 ± 5.3 (1)
After discontinuing the pill	15[b]	30 ± 3.6 (2)
Normotensive pill users	20	16 ± 1.7 (3)
Normotensive women not taking the pill	20	14 ± 1.1 (4)

[a]Values are means ± standard error of the mean. Significance according to Student's *t*-test: $P < 0.02$ for difference between 1 and 3; $P < 0.01$ between 1 and 4; $P < 0.005$ between 2 and 3; $P < 0.001$ between 2 and 4.

[b]No samples were available in five cases.

Prolactin levels were estimated as described elsewhere.[8] All samples were tested in the same assay with an intra-assay variation of 12%. Prolactin values were 3.7 to 28 μg/liter among the 20 women who were not taking the pill.

RESULTS

Subjects with hypertension (blood pressure 160 ± 3/98 ± 2 mm Hg, mean ± SEM) had higher serum prolactin levels than did normotensive pill users or women who were not on the pill (Table 1). There was a positive correlation between the mean prolactin level and the mean arterial blood pressure (Fig. 1). Levels over 28 μg/liter were found in 9 of 20 hypertensive patients (45%) and in 1 of 20 normotensive pill users (5%) ($P < 0.005$, χ^2 test). These higher values were 29 to 96 μg/liter in the hypertensive group and 36 μg/liter in the normotensive group.

After the pill was discontinued the blood pressure of each hypertensive woman dropped to normal (136 ± 4/85 ± 1 mm Hg, mean ± SEM) by the end of the first post-treatment cycle, but the serum prolactin levels remained higher than those of normotensive pill users and those of women who were not taking the pill (see Table 1). An elevated prolactin level (50 μg/liter) was observed 12 months after treatment in one patient.

DISCUSSION

Women whose blood pressure was elevated during oral contraceptive therapy had higher serum prolactin values than did those whose blood pressure remained normal. We do not think that this was due to duration of treatment, which was not significantly longer in pill takers who developed hypertension. In all cases, the hypertension was related to oral contraceptive use, since it appeared during treatment and disappeared after treatment. However, the serum prolactin levels remained elevated in these women even when the blood pressure had returned to normal. The samples were obtained in the afternoon in order to avoid peak levels during early morning hours.

Increased levels of prolactin have been reported in patients with essential hypertension, and bromocriptine treatment suppressed both plasma prolactin and arterial blood pressure.[9] This has been thought to reflect a defect in the central dopamine control mechanism. A correlation between elevated prolactin levels and essential hypertension was observed by Meier et al.[10] only when the blood pressure was measured in the upright position, not in the supine position. In another study,[11] the circulating levels of ethinylestradiol in women with pill-related hypertension were more than twice as high as those in normotensive pill users. Lactotrope stimulation, caused by estrogens, could explain the higher serum prolactin levels in the hypertensive group. No prolactin levels were available prior to oral contraceptive treatment, and it would be of great interest to determine whether women who develop pill-related hypertension have higher starting levels of prolactin.

Although essential hypertension and pill-related hypertension are likely to have differing etiologies, in accordance with the report on essential hypertension[9] our results also suggest that women who develop pill-related hypertension may have a defect in dopaminergic transmission affecting blood pressure and prolactin secretion.

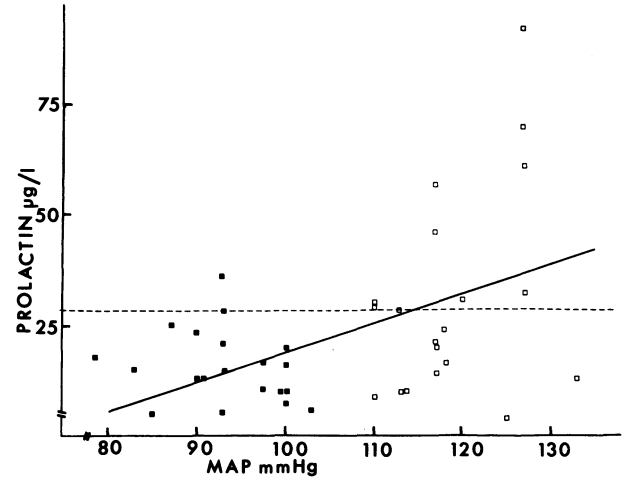

FIG. 1. Correlation between mean arterial blood pressure (*MAP*) and serum prolactin concentration in normotensive (■) and hypertensive pill users (□). The linear equation is $y = 0.59x - 39.6$; correlation coefficient, $r = 0.449$; $P < 0.01$.

Acknowledgments. We thank Professor Tim Chard, M.D., Head, Department of Reproductive Physiology, St. Bartholomew's Hospital Medical College, London, for valuable suggestions about the manuscript; Ms. Anne Mäkelä, Department of Bacteriology and Immunology, University of Helsinki, for technical assistance; and the National Pituitary Agency, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Md., for purified prolactin and the antiserum.

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