

Within two to four months after cessation of treatment, thyroid function tests are normal. Development of thyroid adenomas, hyperthyroidism, and hypothyroidism have not been reported.

ADRENAL FUNCTION

Alterations in adrenocortical function tests observed in patients on combined steroid contraceptives seem to result chiefly from the estrogenic properties of the drugs; there is no evidence of interference with normal pituitary-adrenal relations. Increased protein-binding of aldosterone and cortisol by transcortin (cortisol-binding globulin) is found. Levels of plasma cortisol are increased and the clearance rate of its urinary metabolites is decreased (48, 148). The conclusion that the marked reduction in urinary 17-ketosteroid and 17-ketogenic steroid excretion rates results from impairment of pituitary-adrenal function is based on the reduced response to the metyrapone test during administration of oral contraceptive agents (105, 116). This finding suggests a lack of compensatory increase in pituitary ACTH secretion. The response to the ACTH stimulation test, however, is essentially normal. Furthermore, in the Piromen test, in which the increase in plasma and urinary levels of cortisol and its metabolites presumably results from ACTH secretion, a normal response in the release of ACTH is reported.

Although there are discrepancies among these various studies of the effects of oral contraceptives on adrenal function, there is no evidence to date of adrenocortical insufficiency during surgical procedures or other stress in patients on contraceptive drugs. A possible exception is one clinical report of severe adrenocortical insufficiency associated with the use of oral contraceptives (42).

BLOOD VESSELS

Information regarding the effect of contraceptive steroids on the venous system is limited to clinical observation of increases in the diameter of venous vessels and in venous volume. It remains to be elucidated whether this increase in caliber of the vessels may lead to endothelial injury and exposure of blood to collagen and to the basement membrane. Goodrich and Wood (68) found a significant increase in the distensibility of veins in the calf following administration of contraceptive steroids. This increase was present over the range of venous pressure studied, namely between 5 to 30 mm. mercury and was accompanied by a 25 per cent reduction in mean linear velocity of venous blood flow.

The concentration of angiotensinogen in plasma appears to change consistently following administration of contraceptive steroids. Values up to eight times those of normal have been reported. The rise is observed within 4 days, usually reaching a maximum within 2 weeks. After discontinuation of medication the level may remain elevated for more than a month.

Changes in the concentration of renin are less consistent. It appears that the normal response to an elevation of angiotensinogen is a decrease in renin concentration, suggesting a mechanism of auto-regulation. Because the quantity of angiotensin that can be generated is limited, a large increase in the concentration of angiotensinogen is accompanied by only a twofold increase in angiotensin.

The clinical implications of these changes in the concentrations of angiotensinogen, renin, angiotensin, and aldosterone remain to be elucidated, since the changes are observed in most patients without a concomitant rise in blood pressure. No information is available at present regarding factors predisposing to the adverse effect of contraceptive steroids. They may include renal disease and an increased sensitivity to retention of sodium and water. According to present information, increases in blood pressure of susceptible women caused by contraceptive steroids are reversible even after prolonged use of the drug. It should be noted that elevation occurs in both systolic and diastolic pressures.

It has been suggested that venous hypertension may distend the endothelium of the valve pockets to the point at which injury occurs. Thus, it would be desirable to obtain measurements of venous pressure in peripheral veins in patients on contraceptive steroids and to ascertain whether usual physical activities lead to exceptional increases in venous pressure in excess of those observed in control subjects.