# endocrine and metabolic effects

### Pituitary-Ovarian Function

A considerable number of studies indicate that the oral contraceptives inhibit ovulation by a block at the pituitary level, specifically by inhibition of synthesis or release of LH. During such inhibition, the ovaries tend to become smaller, and changes suggestive of cortical stromal fibrosis have been described. After cessation of the medication recovery is usually prompt, with ovulation resuming in 4 to 8 weeks in most cases. Occasionally, the reappearance of cyclic ovulation may be delayed for several months. Fertility appears to be normal immediately after cessation of the oral contraceptives although a small but unknown number of patients remain amenorrheic. The outcome of pregnancy has been reported to be about the same as in the untreated population with regard to abortion, prematurity, abnormality, and anomaly. There are, however, no prolonged followup studies to ascertain the growth and development of infants born after cessation of therapy. There is no evidence that prolonged suppression of ovulation in nulliparas or multiparas will impair future fertility. The effects of prolonged suppression of ovulation, however, are unknown and require further investigation.

### Pituitary-Adrenal Function

Increased cortisol binding by serum proteins under the influence of oral contraceptives tends to obscure the block of the pituitary ACTH that occurs. Prolonged use of oral contraceptives reduces the response of metopirone but not to ACTH, indicating an inhibition of pituitary ACTH rather than of adrenocortical activity. Recovery of responsiveness occurs in 2 months after cessation of medication. Impaired reaction to stress has not been noted in women on oral contraceptives. There are insufficient data to ascertain the effect of these compounds on women with adrenal insufficiency.

### Thyroid Function

Increased thyroxin-binding globulin has been noted in the majority of women on oral contraceptives. Most, but not all, investigators report a rise in PBI and a decreased $T_3$-RBC uptake. These changes occur rapidly and are maintained for the duration of medication, returning to normal pretreatment levels in about 2 months. The alterations are secondary to the increase in binding proteins produced by estrogens and are similar to those occurring in normal pregnancy. The level of PBI may be in the hyperthyroid range but there is no clinical evidence of hyperthyroidism. If TSH is blocked at the pituitary level, it may be masked by increased protein binding. No precise data are available on this point.

### Carbohydrate Metabolism

Data regarding effects on carbohydrate metabolism in experimental animals and in women are contradictory. Recent studies in women taking oral contraceptives suggest a possible diabetogenic effect of these medications. Abnormal glucose tolerance tests have been observed in as many as 40 percent of women taking oral contraceptives; in women with diabetic family histories, abnormal tests were even more frequent. Plasma insulin levels are above normal in supposedly normal women on oral contraceptives. Some known diabetic women require larger amounts of insulin while on medication. All of these changes tend to regress after discontinuation, and are similar to those seen in normal pregnancy. Whether pregnancy itself is diabetogenic is by no means certain, although diabetes seems to be more prevalent in women of high parity. Whether oral contraceptives can induce diabetes in normal women or even in those predisposed is not known, nor is it clear to what extent the induced changes in carbohydrate tolerance are reversible.

### Liver Function

Many women on oral contraceptives show abnormalities of some liver function tests, especially the BSP and transaminase. A few develop clinical jaundice and evidence of mild hepatic damage, demonstrated by biopsy. These lesions resemble cholestasis of pregnancy. In several women with previous history of cholestasis, these changes have been induced by the oral contraceptives. The abnormal liver function tests revert to normal after cessation of medication.