

Abnormal glucose tolerance is not always reversible. Many women continue to demonstrate abnormalities for months after discontinuing the pills.

It is not known whether the abnormalities will resolve with longer follow-up since none of the women at the time of the study had been off the pills for more than 9 months. Dr. Spellacy's hypothesis of the mechanisms leading to these abnormalities in glucose tolerance seems to argue against improvement in all individuals.

The investigator stressed that not all pills and not all steroids cause the same effects on metabolism. In his studies of growth hormone, insulin, and glucose, he found that norethynodrel caused very significant alterations while chlormadinone caused slight alterations.

Since many of the agents studied use the same estrogen, the metabolic alterations may reflect the action of the various progestins. The higher incidence of abnormalities in women using combination pills indicates that the mechanism is probably dose-related.

The alterations in both carbohydrate and lipid metabolism which are induced by oral contraceptives are different from the alterations seen in pregnancy, Dr. Spellacy said.

During pregnancy, all major lipids are elevated including the nonesterified fatty acids. In women using oral contraceptives, triglycerides are the most significantly elevated, probably as a result of slower breakdown and increased synthesis. The nonesterified fatty acids are not affected by oral contraceptive use. Lysolecithin, a phospholipid which may affect platelet agglutination in the clotting mechanism, is significantly elevated in pill users.

"We can't tell what this means for the individual woman using oral contraceptives," Dr. Spellacy said. "The changes are similar to those which are cautioned against by the cardiovascular specialists."

Dr. Spellacy and his associates attempted to answer five questions concerning the effect of oral contraceptive agents on carbohydrate metabolism: Does the pill alter carbohydrate metabolism? What are the mechanisms involved in carbohydrate alterations by the pills? Do all pills affect this metabolism to the same degree? What are the ultimate risks? And could women at risk be selected prior to the administration of oral contraceptives?

Studies were carried out in women who had never used oral contraceptives but who desire to do so. These women were followed during use of oral contraceptives and following termination of the drugs.

In addition to lipid, growth hormone, and other metabolic determinations, Dr. Spellacy recorded family history, weight changes, previous big babies, babies with birth anomalies, and stillbirths in an attempt to profile a high-risk group.

A preliminary investigation indicated that hormonal alterations in the normal menstrual cycle do not affect carbohydrate metabolism. Abnormal glucose levels were seen after only 19 days of contraceptive use.

Dr. Spellacy found that, after 6 months of therapy, women using combination or sequential oral contraceptives had compensated to bring their glucose levels to normal values, but their insulin levels were increased by 33%.

After 1 year, there was a discrepancy between the two groups of women. Those using a combination agent had slightly elevated glucose levels. In sequential users, glucose levels at 1 year were similar to levels at 6 months. In both groups of women, the insulin levels are still significantly elevated at 1 year.

By 24 months, 4% of the women had abnormal glucose tolerance tests and by 36 months, 12% had abnormal glucose tolerance tests. "These studies indicate that the agents do alter carbohydrate metabolism," Dr. Spellacy said.

He explained that oral contraceptives appear to act on the hypothalamus, perhaps by inhibiting an inhibiting factor to growth hormone.

The result is an increase in human growth hormone release which leads to an increase in blood glucose levels. The increased glucose level stimulates the beta cells of the pancreas to release more insulin.

Initially this sequence compensates for the glucogenic effects of the increased growth hormone. However, there is eventually a failure to compensate. Dr. Spellacy believes that the beta cells eventually, and perhaps permanently, become exhausted.

While this is a probable mechanism for the metabolic alterations seen, it is not the only possibility, he said.