EFFECTS OF LONG-TERM MICRODOSAGE OF NORGESTREL ON GLUCOSE TOLERANCE AND SERUM TRANSAMINASE LEVELS

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Oral contraceptives containing oestrogen and progestagen in high dosage may produce many undesirable side effects. The risk of thrombo-phlebotic episodes (Vessey & Doll, 1969) has caused much concern, but the possible long-term effects of the numerous metabolic changes have also to be considered. Amongst the latter, impaired glucose tolerance (Wynn & Doar, 1969) and increased levels of serum glutamic-pyruvate transaminase (SGPT) have been reported (Larsson-Cohn, 1965).

The use of norgestrel alone, given continuously in low dosage of 50 µg, is slightly less effective as a contraceptive than conventional combinations of oestrogen and progestagen (Foss, Svendsen, Fotherby & Richards, 1968) and 22% of cycles are shorter than 23 days in the women on this regimen, but the incidence of side effects is much lower (Foss, 1968). With the elimination of the oestrogen component, the risk of thrombo-embolic phenomena would appear to diminish.

A long-term investigation on the glucose tolerance and SGPT levels in women receiving 50 µg of norgestrel/day, continuously, for at least a year, was therefore undertaken.

Oral glucose tolerance tests (GTT) were carried out on 103 women (aged 17 to 47) who had been on a regimen of oral contraception with 50 µg norgestrel/day for over a year. After a fast from 22.00 hours on the previous night, initial specimens of venous blood were taken, followed by the loading dose of 50 g glucose in 100 ml water. Subsequent venous samples were collected after $\frac{1}{4}$, 1 and $1\frac{1}{2}$ or 2 hr. Blood glucose was estimated on the AutoAnalyzer (Technicon Instruments Co. Ltd, Chertsey, England) by a ferricyanide reduction technique, using a slight modification of the Technicon N. methodology.

Any unusual tolerance curve was repeated with 100 g glucose and continued for $2\frac{1}{2}$ hr.

The results of the GTT have been compared with those obtained by Boyns, Crossley, Abrams, Jarrett & Keen (1969) on sixty-four untreated women in a normal population sample, aged 24 to 44 years. Their subjects were instructed to take extra carbohydrate for 3 days and the oral glucose load equivalent to
50 g glucose was given as Lucozade. Apart from this slight difference in preparation, these authors employed an automated blood glucose method similar to the one used in this study.

In addition, venous blood was collected, at the same time as the fasting specimen, for estimation of SGPT. The enzyme was estimated by the method of Karmen (1955).

In Text-fig. 1, the mean results of the GTT in the group of 103 norgestrel-treated patients are compared with the results reported by Boyns et al. (1969). If anything, glucose tolerance is higher in the treated group than in the group receiving no treatment.

**Text-fig. 1.** Glucose tolerance in 103 women on continuous microdosage with norgestrel (50 µg/day for over 1 year) compared with values in sixty-four untreated women of the same age group, found by Boyns et al. (1969). ●, Women receiving norgestrel; ○, untreated women.

Ten of these GTT showed an unusual pattern and were repeated, giving a loading dose of 100 g glucose. Seven of these then showed flat curves with 2-hr values below the fasting level; the other three showed a normal response to glucose after 30 min and a sub-fasting level at $2\frac{1}{2}$ hr.

In Text-fig. 2, the mean results of GTT performed on women at the same stage of the menstrual cycle are plotted. The results show a tendency to an increased impairment of glucose tolerance as the cycle progresses. Significant differences in the mean results were found in the 2-hr blood specimens, between Days 0 to 5 and 11 to 16, 0 to 5 and 17 to 28, 6 to 10 and 11 to 16, and 6 to 10 and 17 to 28 ($P<0.01$ in all cases).

The mean of the SGPT levels for these patients was 30 (S.D. 10) and for comparison, the mean for sixty-five blood transfusion donors, male and female of the same age-group, was 35 (S.D. 12.5). There were no significant differences between the mean SGPT levels of the groups.

With the combination of oestrogens and progestagens available for oral contraception, it would appear that, if the dose is high, there may be a diabetogenic effect (Pi-Sunyer & Oster, 1968); but smaller dosage combinations may even increase glucose tolerance (Clinch, Turnbull & Khosla, 1969). Gershberg, Javier & Hulse (1964) stated that oestrogen was the major cause of metabolic
changes, but that progestagen might exert an additional effect if converted to oestrogenically active substances. Norgestrel itself is not oestrogenic, nor is it converted to oestrogen in vivo (Edgren, Jones, Clancy & Nagra, 1968) and so, when it is given continuously in microdosage of 50 µg/day, it could be predicted that no impairment of glucose tolerance would occur. These investigations of continuous therapy for over a year, and in some patients for 3½ years, suggest that there is no diabetogenic effect.

The variation of glucose tolerance with the stages of the menstrual cycle while on continuous norgestrel (50 µg/day) follows the pattern described by Jarrett & Graver (1968) in women receiving no oral contraceptives. The presence of this normal cyclical pattern in the women treated with norgestrel may be interpreted as further evidence that this drug produces no impairment of glucose tolerance. However, the sub-fasting level of blood glucose at 1½ and 2 hr may indicate some effect of hyperinsulinism and further studies are currently proceeding to elucidate this.

The finding of normal SGPT levels in all women in this trial contrasts with those of an earlier series in which 7% of subjects receiving norethindrone and mestranol had raised serum enzyme levels (Larsson-Cohn, 1965). Our observations suggest that norgestrel, in continuous daily microdosage of 50 µg does not have the effect, usually ascribed to the combinations of oestrogen and progestagen, of decreasing glucose tolerance or raising the levels of serum transaminase.

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REFERENCES


