Oral contraception in diabetic women.

Diabetes control, serum and high density lipoprotein lipids during low-dose progestogen, combined oestrogen/progestogen and non-hormonal contraception

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Abstract. Thirtyeight women with insulin-dependent diabetes were randomly allocated to contraception with either a progestogen only (Lynestrenol 0.5 mg daily) (LYN), a combined oral contraceptive (OC) (Ethinyl oestradiol 50 μg + Lynestrenol 2.5 mg) (EE + LYN) or a non-hormonal intrauterine device (IUD). Diabetes control (i.e. insulin dosage, blood and urinary glucose and body weight) and the lipid concentration in serum and in high density lipoprotein (HDL) were assessed before and during six months use of the respective contraceptives.

In the LYN group urinary glucose excretion increased 10% in spite of unchanged blood glucose, body weight and insulin requirement. All serum lipids decreased; triglycerides by 40% (P < 0.01), cholesterol by 13% (P < 0.01) and phospholipids by 12% (P = 0.06), without alteration of HDL lipids. In the group using combined OC (EE + LYN) the insulin requirement increased by 7% (P < 0.01) without any change in body weight or blood and urinary glucose. Serum as well as HDL lipids remained unchanged. In the IUD group neither diabetes control nor serum or HDL lipids were altered.

It is concluded that in insulin-dependent diabetics the progestogen (LYN) has little influence on diabetes control but has a marked, though probably not adverse, effect on lipid metabolism. The combined OC (EE + LYN) may impair glucose homeostasis slightly but has little influence on serum or HDL lipids. These findings seem to differ from those obtained in non-diabetics during administration of contraceptive steroids and these differences suggest that absence of endogenous insulin production enhances the effects of progestogen and reduces the effects of synthetic oestrogens on lipid metabolism.

The optimal method of contraception for young insulin-dependent diabetics has not yet been established. The well-known drawbacks of intrauterine devices (IUDs) in nulliparous women (Weström et al. 1976), in addition to their low efficacy in diabetics (Wiése & Osler 1974; Steel & Duncan 1978), have increased the need for hormonal contraception in these patients. However, because of a reported high incidence of coronary and cerebrovascular disease in young diabetics using even 'low-oestrogen' oral contraceptives (OC) (Steel & Duncan 1978), the effect of progestogens only warrants elucidation.

Both oestrogen-containing OCs, and progestogens only have been shown to diminish glucose tolerance in subclinical diabetics (Engelhardt et al. 1975; Goldman & Eckerling 1970).

In insulin-dependent diabetics, combined OCs may increase the insulin requirements in some, but not all patients (Zeller et al. 1974). The effects of low-dose progestogens in insulin-dependent diabetics appear not to have been investigated before.

In non-diabetic women some combined OCs have produced, presumably undesirable, atheros-
clerosis-associated serum lipid changes (Miller & Miller 1975; Rössner et al. 1978) such as increased serum triglycerides, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) lipids as well as decreased levels of high density lipoprotein lipids (HDL) (Arntzenius et al. 1978; Wynn et al. 1979). Increased serum triglycerides is a dose-dependent effect of oestrogens and the lowered HDL is thought to be a progestogen effect (Goldzieher et al. 1978; Larsson-Cohn et al. 1979; Silfverstolpe et al. 1979).

Women pre-disposed to diabetes are more prone to develop some of these lipid alterations than non-diabetics (Hassing-Nielsen 1974). For obvious reasons, the influence of sex hormones on lipid metabolism in insulin-dependent diabetics has been little elucidated although qualitative difference as compared with the effects in non-diabetics have been postulated (Beck et al. 1976).

The aim of this study was therefore to evaluate the effect on diabetes control and serum and HDL lipids in insulin-dependent diabetics during six months administration of a low dose progestogen only (Lynestrenol 0.5 mg) (LYN), and a combined OC (Ethinyl oestradiol 50 μg + Lynestrenol 2.5 mg) (EE + LYN) as compared with non-hormonal contraception (IUD).

Patients and Methods

Patients

Thirtyeight women with insulin-dependent diabetes mellitus consulting the diabetes clinic of the Department of Obstetrics and Gynecology at Sahlgrenska sjukhuset, University of Göteborg, for contraceptive advice were invited to participate in the study. The distribution of the study groups by mean age, parity and duration of diabetes is shown in Table 1, as well as the distribution according to White’s classification (White 1965). No subject had a history of hepatic or endocrine disease other than diabetes, and all were non-diabetics and had normal serum creatinine. The women were more than two months post-partum, non-lactating and had not been taking any medication known to influence lipid metabolism, except for insulin, during a period of at least two months before entering the study.

Protocol

The 25 subjects who volunteered for hormonal contraception were randomly divided into two groups, one of which was given a continuous low-dose progestogen (LYN) daily and the other a combined OC (EE + LYN) from the 5th to the 27th day of the menstrual cycle. Those who did not accept hormonal treatment, or in whom oral contraceptives were contraindicated (as in two women with a history of recurrent superficial thrombophlebitis) were allocated to contraception with an IUD (Cu T 200).

Indices of diabetes control, i.e. current insulin dose, fasting blood glucose, 24-hour urinary glucose excretion and body weight index (% of normal according to height, Lindberg et al. 1956), were evaluated in the last week of the two cycles preceding onset of medication or IUD insertion and the last week of cycle one, three and six during the use of the respective contraceptives.

Venous blood samples for lipid analysis were drawn at 8 p.m., after an overnight fast, in the last week of the cycle preceding the start of contraceptive treatment and

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>23.9 ± 3.8</th>
<th>25.8 ± 5.0</th>
<th>29.7 ± 5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td>0.9 ± 0.8</td>
<td>1.7 ± 1.0</td>
<td>1.5 ± 1.1</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>10.3 ± 5.9</td>
<td>10.8 ± 7.9</td>
<td>13.3 ± 7.6</td>
</tr>
<tr>
<td>White’s classes (number of patients)</td>
<td></td>
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</tr>
<tr>
<td>B</td>
<td>3</td>
<td>3</td>
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<tr>
<td>C</td>
<td>5</td>
<td>7</td>
<td>6</td>
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<td>D to F</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1.

Mean age (± sd), parity, duration of diabetes and distribution according to White’s classification in insulin-dependent diabetic women using Lynestrenol 0.5 mg (LYN), ethinyl oestradiol 50 μg + Lynestrenol 2.5 mg (EE + LYN), or an intrauterine device (IUD) as a contraceptive for 6 months.
in the last week of the sixth treatment cycle. The blood was centrifuged and the serum immediately recovered, frozen and stored at −20°C until analysis.

**Laboratory methods**

Blood and urinary glucose were determined by a glucose oxidase method (Levin & Linde 1962). Lipids were determined in whole serum and in HDL: cholesterol according to Cramér & Isaksson (1959), triglycerides as glyceride-glycerol (Carlsson 1959) and phospholipids as lipid phosphorus (Svanborg & Svennerholm 1961). The HDL-fraction was obtained after Heparin-Mn Cl₂ precipitation of VLDL and LDL according to the method of Burstein et al. (1970).

**Statistical methods**

Individual means of pre-treatment and treatment values of diabetes control were analysed as paired observations with Student’s t-test and Wilcoxon’s signed rank test. As in other series the lipids were significantly skewed but could be approximately normally distributed by logarithmic transformation before analysis with Student’s t-test. Wilcoxon’s signed rank test on original data gave identical results. P-values < 0.05 were considered significant.

**Results**

### Clinical observations

No symptoms or signs of thromboembolic incidents or visual disturbances were observed in any of the groups. Neither mean blood pressure, blood haemoglobin concentration, nor body weight (absolute or relative weight index) changed during the use of any of the three contraceptives.

In the low-dose LYN group 4 out of 12 subjects complained of intolerable menometrorrhagia or amenorrhoea while only 1 out of 13 in the group with combined EE + LYN treatment had any complaints about cycle control. In the groups using the IUD, 2 out of 13 subjects complained of menometrorrhagia and three subjects of abdominal pain or severe dysmenorrhoea. One clinically diagnosed salpingitis was recorded.

### Diabetes control (Table 2)

None of the women in any of the groups had any marked deterioration of their diabetes control. Minor adjustments of insulin doses were necessary in the two groups on oral contraception.

In the group treated with low-dose LYN neither the mean insulin dose nor the fasting blood glucose level changed but mean 24-hour urinary glucose excretion increased by 43% (P < 0.05).

In the group taking the combined EE + LYN contraceptives the mean insulin requirement increased by 7% or 2.5 units (P < 0.01), without any change in fasting blood glucose or urinary glucose excretion.

In the **IUD**-group there were no changes in diabetes control.

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### Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Insulin requirement (units/day)</th>
<th>Urinary glucose (mmol/24 h)</th>
<th>Blood glucose (mmol/l)</th>
<th>Weight index (% of normal)</th>
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<tr>
<td><strong>LYN</strong> <em>(n = 12)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>49.1 ± 4.5</td>
<td>202 ± 45</td>
<td>11.0 ± 1.0</td>
<td>95.1 ± 2.3</td>
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<tr>
<td>During</td>
<td>47.0 ± 3.6</td>
<td>289 ± 64*</td>
<td>11.7 ±</td>
<td>94.5 ± 2.5</td>
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<tr>
<td><strong>EE + LYN</strong> <em>(n = 13)</em></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Before</td>
<td>33.2 ± 3.1</td>
<td>229 ± 49</td>
<td>10.3 ± 1.4</td>
<td>92.7 ± 3.3</td>
</tr>
<tr>
<td>During</td>
<td>35.8 ± 3.5**</td>
<td>248 ± 48</td>
<td>10.6 ± 1.1</td>
<td>92.2 ± 3.3</td>
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<tr>
<td><strong>IUD</strong> <em>(n = 13)</em></td>
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<tr>
<td>Before</td>
<td>32.3 ± 2.8</td>
<td>168 ± 62</td>
<td>11.1 ± 1.0</td>
<td>92.1 ± 1.8</td>
</tr>
<tr>
<td>During</td>
<td>32.4 ± 3.0</td>
<td>151 ± 110</td>
<td>10.0 ± 1.1</td>
<td>92.4 ± 1.7</td>
</tr>
</tbody>
</table>

* = P < 0.05. ** = P < 0.01.
Influence on lipid content (mmol/l) in serum and high density lipoprotein (HDL) in insulin-dependent diabetic women using either Lynestrenol 0.5 mg (LYN), ethinyl oestradiol 50 µg + Lynestrenol 2.5 mg (EE + LYN) or an intrauterine device (IUD) as a contraceptive for 6 months (mean ± SEM).

<table>
<thead>
<tr>
<th></th>
<th>Serum</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cholesterol</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>LYN (n = 12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>5.4 ± 0.2</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>During</td>
<td>4.5 ± 0.2**</td>
<td>0.5 ± 0.0**</td>
</tr>
<tr>
<td>EE + LYN (n = 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>5.2 ± 0.4</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>During</td>
<td>4.9 ± 0.3</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>IUD (n =13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>5.5 ± 0.4</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>During</td>
<td>5.4 ± 0.5</td>
<td>0.8 ± 0.1</td>
</tr>
</tbody>
</table>

* = P ≤ 0.05. ** = P < 0.01.

Serum and HDL lipids (Table 3)

In the low-dose LYN group there were marked reductions in serum lipids. Triglycerides decreased by 43% (P < 0.01), cholesterol by 13% (P < 0.01) and phospholipids by 12% (P = 0.06), while HDL lipids remained unchanged.

In the group taking the combined OC, EE + LYN, no significant changes of any of the serum or HDL lipid concentrations were recorded. No lipid or lipoprotein changes were found in the IUD group.

Discussion

In this study of young, insulin-dependent diabetics six month's medication with the low-dose progestogen LYN (a 19-nor-testosterone derivative) caused no change in mean insulin dosage, fasting blood glucose levels or body weight, although there was an increase (P < 0.05) in mean urinary glucose excretion. This latter finding was to some extent due to underdosage of insulin, probably indicating general difficulty in the clinical assessment of the insulin requirement during progestogen administration. Our results thus show that this low-dose progestogen does not have the serious clinical consequences reported by Lebherz & Fobes (1961) who administered higher doses of progestogens in the treatment of endometriosis.

During administration of the combined OC, EE + LYN, 5 out of 13 women required moderately higher insulin doses and consequently the mean insulin dosage increased by 7% without alteration of any of the other indices of diabetes control.

These findings are in agreement with earlier studies on long-term administration of combined OC (Zeller et al. 1974), reporting increased insulin requirement in about one-third of diabetic women, and are also in line with data indicating impaired glucose tolerance in normal (Waldbaum et al. 1969; Wynn et al. 1979) and subclinically diabetic women (Engelhardt et al. 1975) taking similar preparations of synthetic oestrogens and 19-nor-testosterone-type progestogens. Thus, the findings of a possibly impaired glucose homeostasis during low-dose LYN administration and also a slightly increased insulin requirement during combined EE + LYN medication support the view that 19-nor-testosterone derivatives increase 'peripheral insulin resistance' (Spellacy et al. 1973; Wynn et al. 1979) and consequently have a diabetogenic effect in women with limited reserves for insulin production (Goldman & Eckerling 1970). Our results also suggest this effect to be dose-dependent and/or potentiated by simultaneously administered synthetic oestrogens.
As regards changes in serum and HDL lipid concentration, the most striking finding during LYN administration was a marked reduction in serum triglycerides concomitant with slight reductions in serum cholesterol and phospholipids (without changes of HDL lipids). The triglyceride lowering effect of 19-nor-testosterone derivatives has been well documented in subjects with hyperlipidaemia (Glueck et al. 1971) and especially in oestrogen-induced hypertriglyceridaemia (Goldzieher et al. 1978). In normolipidaemic women, on the other hand, the effect of low-dose progestogens on serum triglycerides has been less consistent but serum triglycerides are usually reduced when women are studied during the first six months after a pregnancy (Spellacy et al. 1973). In this series all but one woman in the LYN-treated group had normal pre-treatment levels of serum triglycerides and the mean triglyceride reduction during LYN administration was not different after exclusion of this hypertriglyceridaemic woman or those two women who had been pregnant less than six months before the first sampling. An additional argument against the view that the lipid lowering effects of progestogens only reflects post-partum metabolic adaptations is the fact that there were no changes in serum triglycerides in the IUD group, which contained an identical proportion of recently pregnant subjects.

The lack of influence on serum and HDL lipids of EE + LYN in these diabetics is in contrast to the oestrogen dose-dependent elevation of serum triglycerides seen in non-diabetic women during administration of similar OC-formulations (Wynn et al. 1979). Our findings thus suggest that, in insulin-dependent diabetics, combined OC do not have the same hypertriglyceridaemic effect as in non-diabetics and in women predisposed to diabetes (Hassing-Nielsen 1974; Rådberg et al., to be published). Our results, confirming over a longer time-span the findings of Beck et al. (1976), suggest that a concomitant endogenous insulin production is a prerequisite for oestrogen-induction of hypertriglyceridaemia, and/or that the progestogen-induced lipid-lowering effect is enhanced by the lack of endogenous insulin. In non-diabetics, triglyceride kinetic studies (Kissebah et al. 1973) have revealed that oestrogens increase the secretion of triglyceride-rich VLDL-particles while progestogens enhance their removal. In insulin-treated diabetics with hypertriglyceridaemia, however, interrelations of VLDL production and removal are less well understood (Nikkilä et al. 1977). It is therefore tempting to assume that progestogens may impair lipogenesis in these patients in addition to their ability to enhance triglyceride removal.

As regards HDL-cholesterol and phospholipids, neither LYN nor EE + LYN caused the decrease seen in non-diabetics after administration of OC formulations of the same type (Arntzenius et al. 1978; Larsson-Cohn et al. 1979) as well as progestogens (Silfverstolpe et al. 1979). However, in this series, the women using hormonal contraception had relatively low pre-treatment HDL cholesterol levels and any influence of progestogens might therefore be less pronounced. Thus, the lack of effect on HDL in these diabetics does not preclude such an effect in non-diabetics. However, the stable diabetes control and serum lipid levels in the IUD group (our control group) argue against any major influence of the experimental design on non-steroid related factors affecting HDL (see review by Witzum & Schonfeld 1979).

It thus seems justified to conclude that neither low-dose LYN nor the combined EE + LYN treatment had any dramatic influence on diabetes control although both preparations may impair glucose homeostasis slightly. Furthermore, neither of the oral contraceptives produced any lipid changes (e.g. lowering of HDL-cholesterol or hypertriglyceridaemia) associated with early development of atherosclerotic manifestations in non-diabetic subjects (Miller & Miller 1975; Rössner et al. 1978) and in diabetic women (Gordon et al. 1977).

The reported high incidence of vascular accidents in insulin-treated diabetics during oral contraception (Steel & Duncan 1978) therefore appears not to be primarily related to lipoprotein changes induced by these steroids.

Since the genital side effects (e.g. poor cycle control and infections) of low-dose LYN and IUD appear to be at least as frequent in diabetics as in non-diabetics, it is suggested that the undoubtedly more efficient combined OC (e.g. EE + LYN) should be considered also for insulin-dependent diabetics, particularly for young nulliparous women.

References


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