Hormonal Contraception in Women With IDDM

Influence on glycometabolic control and lipoprotein metabolism

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OBJECTIVE — Safe and effective contraceptive methods are essential for women with insulin-dependent diabetes mellitus (IDDM), but opinions on the use of hormonal oral contraceptives by these women are conflicting. We evaluated the effects on glycometabolic control and lipoprotein metabolism in women with IDDM treated with an oral contraceptive not previously studied in a diabetic population.

RESEARCH DESIGN AND METHODS — A total of 22 women with IDDM received a monophasic combination of ethinyl estradiol and gestodene for 1 year; 20 women of comparable diabetic status using nonhormonal contraception were selected as control subjects. Evaluation was performed before and after 1, 3, 6, and 12 months of hormonal intake using nonparametric statistical methods.

RESULTS — Except for a higher median age of the control group, the baseline values for all clinical and metabolic variables were similar in the two groups, and in neither of the groups were changes in blood pressure, body mass index, or glycemic control observed. In the oral contraceptive group, decreased serum levels of low-density lipoprotein (LDL) cholesterol and increased levels of triglycerides and lipoprotein A were noted, whereas total cholesterol and high-density lipoprotein cholesterol levels were unchanged. In the control group, a decrease of LDL cholesterol was observed. No effect of tobacco smoking on glycometabolic control or lipoprotein metabolism could be demonstrated during hormonal intake.

CONCLUSIONS — No evidence of impaired glycometabolic control or adverse changes in serum levels of lipoproteins known to be associated with atherosclerosis was observed in women with well-controlled IDDM during 1 year of oral contraception with ethinyl estradiol and gestodene.

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BMI, body mass index; HDL, high-density lipoprotein; IDDM, insulin-dependent diabetes mellitus; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

The demonstration that optimal glycometabolic control at conception and during early pregnancy may reduce the risk of spontaneous abortions and congenital malformations has emphasized the importance of contraception as an integrated part of the care of fertile diabetic women (1,2). Although knowledge of the use of contraceptive methods among women with diabetes is scarce, their contraceptive practice probably reflects that of the nondiabetic population (3). If the tendency for increased use of oral contraceptives containing the new gonane progestogens (gestodene, desogestrel, and norgestimate) observed in the general population during the last decade is extended to the diabetic population, it is necessary to evaluate their effects on the metabolic status of diabetic women, who have proven to be highly susceptible to the effects of exogenous sex steroids (4,5).

In this controlled trial, we studied glycemic control and lipoprotein metabolism in a group of women with insulin-dependent diabetes mellitus (IDDM) in good metabolic control during long-term intake of an oral contraceptive containing ethinyl estradiol in monophasic combination with the gonane progestogen gestodene. This compound has proven to exert only minor effects on carbohydrate and lipoprotein metabolism in nondiabetic women (6), but it has not previously been evaluated in women with IDDM.

RESEARCH DESIGN AND METHODS

Study population and experimental design

A total of 45 Caucasian women with IDDM volunteered to participate in the study. According to White's classification (7), all women belonged to class B or C (no vascular or renal complications present), and none of the participants had previously suffered from liver disease or thromboembolic disorders. All women were at least 6 months postpartum or 3 months postabortem, and none were lac-

tating. All had regular menstrual periods, and in case of previous use of oral contraceptives, a washout period of 3 months was required. Informed consent was obtained from all participants, and the study was approved by the Medical Ethics Committee of Copenhagen and the Danish National Board of Health.

The participants were recruited from women with IDDM attending our outpatient clinic for contraceptive counseling. The women recruited had all had IDDM for at least 2 years (median 10.5 years) and were all in stable glycemic control. Women who wanted to use oral contraception were asked to participate in the study, and upon acceptance they received a monophasic combination of 30 μg ethinyl estradiol and 75 μg gestodene, which was taken cyclically for 21 days followed by 7 days that were free of medication for 12 consecutive cycles. For each participant in the oral contraception group, a woman of similar age, diabetic status, smoking habits (only women smoking <10 cigarettes/day were included), body mass index (BMI), and marital and socioeconomic status using nonhormonal contraception was selected as a control subject.

Assessment of endothelial function and evaluation of cardiovascular risk factors have been performed in a subgroup of the study population comprising 11 women from the oral contraception group and 12 women from the control group. The clinical characteristics and variables reflecting glycemic control of this subgroup have previously been reported (8,9).

One woman from the oral contraception group (for whom no control subject had been selected) and two women from the control group withdrew their consent before baseline values were obtained and were not replaced. One woman from the control group conceived after 4 months, and five participants from the treatment group did not complete the study period. Three of these women left the study after 3 months, two for personal reasons and one because of increased frequency and severity of hypoglycemic attacks. Two women left the study after 6 months of treatment because of abdominal discomfort and nausea.

Blood collection

In all participants, evaluation of glycometabolic control and lipoprotein metabolism was performed in the luteal phase of the menstrual cycle after inclusion. In the treatment group, the evaluation was repeated during the last 10 days of pill intake in treatment cycles 1, 3, 6, and 12. The control group was evaluated in the luteal phases of corresponding cycles. Venous blood samples were collected between 8:00 and 9:00 A.M., before morning insulin injection, after an overnight fast and abstinence from smoking. Blood was drawn from an antecubital vein with a minimum of stasis after 15 min of supine rest, using evacuated glass tubes and 20-gauge needles and omitting the first few milliliters from analysis. Blood samples for glucose and HbA_{1c} analysis were drawn in 3-ml tubes containing 0.05 ml of 0.1 mol/l dipotassium EDTA (Exetainer, Labco, High Wycombe, U.K.). Blood for analysis of total cholesterol, high-density lipoprotein (HDL) cholesterol (including the subfractions HDL_2 cholesterol and HDL_3 cholesterol), apolipoproteins A and B, and triglycerides was drawn in evacuated tubes (Venoject, Terumo, Leuven, Belgium).

Blood analysis

Plasma glucose (normal range 3.3–5.5 mmol/l) was determined by a standard dehydrogenase method (10), and all participants were instructed to measure their blood glucose six times daily (at 7:00 A.M. [fasting], 8:30 A.M., 12:00 noon, 4:30 P.M., 8:00 P.M., and 10 P.M.) during the 2 days preceding the control visits using a HypoCount II home monitor (Hypoguard, Suffolk, U.K.) and Haemo-glucotest 1–44 test strips (Boehringer Mannheim, Mannheim, Germany). The values were averaged and are expressed as 24-h blood glucose level. Long-term glycemic control was assessed by HbA_{1c} (normal range 4.1–6.4%) levels, which were analyzed by a chromatographic technique (Diamat, Bio-Rad, Richmond, CA). Urine albumin concentration was measured in two consecutive morning urine samples by a turbidimetric method (Behring TurbiTime System, Behringswerke, Marburg, Germany; detection limit 6 mg/l), and a nocturnal urinary albumin excretion of >30 μg/min was considered indicative of incipient nephropathy (microalbuminuria) (11).

Total cholesterol and triglyceride levels (normal ranges 3.6–6.8 and 0.50–2.20 mmol/l) were determined enzymatically (Roche, Basel, Switzerland). HDL cholesterol (normal range 0.85–1.97 mmol/l) was measured after precipitation of low-density lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) cholesterol with $MgCl_2$. The fractions of HDL cholesterol, HDL_2 cholesterol, and HDL_3 cholesterol were determined according to Talameh et al. (12). The VLDL cholesterol level (normal range 0.23–1.00 mmol/l) and LDL cholesterol concentration (normal range 1.7–5.4 mmol/l) were calculated as previously described (6), and apolipoproteins A and B (normal value 1.15–2.2 and 0.6–1.5 g/l) were determined enzymatically (Boehringer Mannheim).

Arterial blood pressure was measured with a standard clinical sphygmomanometer (cuff size 12 × 25 cm). The mean arterial blood pressure was calculated as the diastolic pressure + 1/3 × (systolic pressure − diastolic pressure). Body weight is expressed as BMI (kg/m^2).

Statistical analysis

Before the study, the size of the study population was calculated by means of the SD of our reference values for serum levels of cholesterol (0.90 mmol/l). Because we wanted the smallest difference between the baseline values and the treatment values not to be overlooked to be 1 mmol/l, we needed 17 women in each group, as a risk of type 1 error of 5% and a risk of type 2 error of 10% was accepted.

The laboratory tests were all run

Table 1—*Changes in blood pressure, BMI, and glycometabolic control in 22 women with IDDM before and during 12 months of treatment with a monophasic combination of 30 μg ethinyl estradiol and 75 μg gestodene and in 20 women with IDDM before and during 12 months of observation (control subjects)*

	Oral contraception		Control subjects	
Variable	Before	During	Before	During
Mean arterial blood pressure (mmHg)	90 (80–103)	92 (79–109)	97 (75–113)	94 (81–111)
BMI (kg/m^2)	22.5 (19.1–25.4)	22.4 (19.2–25.3)	22.7 (17.9–31.6)	22.5 (19.1–30.9)
Fasting plasma glucose (mmol/l)	9.9 (1.8–19.7)	11.6 (4.7–18.1)	10.5 (5.2–22.6)	12.4 (4.5–19.4)
HbA_{1c} (%)	8.2 (5.8–11.2)	8.4 (6.0–10.8)	8.5 (6.4–11.7)	8.2 (7.3–11.0)
24-h blood glucose level (mmol/l)	8.7 (4.2–16.9)	9.3 (5.2–14.8)	7.5 (5.4–13.3)	8.5 (7.0–11.6)
Daily insulin requirement (IU)	41 (22–70)	41 (27–70)	42 (16–58)	42 (22–58)
Microalbuminuria	2	2	3	2
Free fatty acids (mmol/l)	0.88 (0.16–2.40)	0.86 (0.22–1.42)	0.89 (0.32–2.52)	1.11 (0.53–1.69)

Data are medians (range) or *n*. This table includes data that have been published separately for 11 women from the oral contraception group and 12 women from the control group (8, 9).

in duplicate, and the results for each variable are expressed by the mean. Differences between the two groups were evaluated by the Mann-Whitney *U* test. To evaluate the effect of hormonal intake, the five serial measurements of each variable in both groups were evaluated by Friedman's analysis of variance, and in case of significant results, differences within the groups were evaluated by Wilcoxon's rank-sum test to compare appropriate periods. Spearman's test was used in the evaluation of covariation. Two-tailed *P* values < 0.05 (2 alpha) were considered statistically significant.

RESULTS

Clinical characteristics and glycemic control

The median age of the control group (28.5 years, range 21–33 years) was significantly higher than that of the oral contraceptive group (26.5 years, range 19–32), and a corresponding difference in the duration of diabetes was noted (control group: 11.5 years, range 2–25 years; oral contraceptive group: 9.5 years, range 3–22 years). Eleven women in the oral contraceptive group and nine in the control group were smokers. The smoking habits of the participants were unchanged during the study period. In Table 1, the average values obtained during treatment (or observation period) are compared with the baseline values. The mean arterial blood pressure and BMI were unchanged in both groups.

In the oral contraceptive group, we observed a difference between the baseline and the treatment values for fasting glucose of 1.7 mmol/l ($P = 0.55$); because the SD of this variable was 5.59 mmol/l, an analysis of the statistical power results in a risk of overlooking an existing difference (type 2 error) of 84%, given a risk of type 1 error of 5%. In addition, the 24-h blood glucose profile, HbA_{1c}, daily insulin requirement, and free fatty acids showed no statistically significant changes during hormonal treatment. Stable values were also noted in the control group. Five women, two of whom were smokers, had microalbuminuria at the start of the study; in one woman, this initial finding could not be confirmed on later measurements, and none of the participants developed increased urine albumin excretion during the study period.

Lipids and lipoproteins

The values for lipids and lipoproteins are shown in Tables 2 and 3. The values for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides for a subgroup of the study population composed of 11 women from the oral contraception group and 12 women from the control group have previously been reported (9). When the baseline values of the two groups were compared, we found no changes of statistical significance. In the treatment group, we observed unchanged levels of total cholesterol, but significant fluctuations within the cholesterol-containing lipoprotein fractions were noted. The concentration of LDL cholesterol decreased, whereas elevated levels of HDL cholesterol, due to increased HDL_3 cholesterol levels, were observed. Triglyceride and VLDL cholesterol levels also increased during hormonal intake, and within the apolipoproteins we observed increased levels of apolipoprotein A, while the apolipoprotein B concentration was unchanged. In the treatment group, three women (two of whom had increased urine albumin excretion) had elevated levels of total cholesterol due to increased LDL cholesterol concentration at baseline. In two of the women, the concentrations fell to the normal range after hormonal treatment was started, whereas the hypercholesterolemia persisted in one woman with microalbuminuria. Elevated levels of triglycerides were observed in one woman throughout the study period.

In the control group, we also observed a decrease in LDL cholesterol con-

Table 2—*Concentrations of lipids and lipoproteins before and during 12 months of treatment with a monophasic combination of 30 μg ethinyl estradiol and 75 μg gestodene in a group of 22 women with IDDM*

Variable	Baseline	1 month	3 months	6 months	12 months
n	22	22	22	19	17
Total cholesterol (mmol/l)	4.93 (3.06–7.97)	4.64 (3.19–6.32)	4.64 (3.44–7.51)	4.74 (3.10–6.93)	4.53 (3.09–6.52)†
LDL cholesterol (mmol/l)	3.16 (1.41–6.37)	2.56 (0.98–4.52)	2.55 (1.11–4.60)	2.55 (0.52–4.83)*	2.46 (0.92–4.44)*
HDL cholesterol (mmol/l)	1.36 (0.95–2.12)	1.43 (1.11–2.07)	1.47 (0.88–1.98)	1.47 (1.06–2.13)	1.52 (1.14–2.21)†
HDL_2 cholesterol (mmol/l)	0.64 (0.14–1.22)	0.67 (0.25–1.09)	0.59 (0.11–1.17)	0.67 (0.20–1.23)	0.50 (0.20–1.18)†
HDL_3 cholesterol (mmol/l)	0.75 (0.52–1.03)	0.80 (0.59–1.10)*	0.86 (0.63–1.15)*	0.88 (0.60–1.12)*	1.00 (0.84–1.19)*
HDL cholesterol/total cholesterol	0.31 (0.13–0.50)	0.33 (0.18–0.58)	0.33 (0.15–0.53)	0.33 (0.19–0.69)	0.34 (0.18–0.57)†
VLDL cholesterol (mmol/l)	0.41 (0.18–2.76)	0.47 (0.26–1.12)*	0.56 (0.26–0.88)*	0.53 (0.39–2.01)*	0.51 (0.40–1.67)*
Triglycerides (mmol/l)	0.88 (0.39–5.98)	1.03 (0.57–2.43)*	1.23 (0.57–1.92)*	1.14 (0.84–4.37)*	1.10 (0.86–3.61)*
Apolipoprotein A (g/l)	1.24 (1.04–1.62)	1.38 (1.02–1.71)*	1.38 (1.07–1.74)*	1.39 (1.14–1.92)*	1.40 (1.12–1.82)*
Apolipoprotein B (g/l)	0.86 (0.48–2.05)	0.87 (0.45–1.51)	0.92 (0.47–1.85)	0.86 (0.48–1.39)	0.91 (0.39–1.43)†

Data are medians (range). This table includes data that have been published separately on total cholesterol, HDL and LDL cholesterol, and triglycerides for 11 women (9). * Baseline values vs. treatment values: $P < 0.05$. † Baseline values vs. treatment values: NS.

centration. The level of HDL cholesterol was unchanged, despite an increase in the HDL_3 cholesterol fraction. The concomitant decrease in total cholesterol (although not statistically significant) resulted in an increased HDL cholesterol: total cholesterol ratio, as in the treatment group. No other changes of statistical significance were noted in the control group. In the control group, one woman (without microalbuminuria) had persistent elevated levels of total and LDL cholesterol, but triglyceride levels were within the normal range in all the women.

We observed a negative correlation between the daily insulin requirement and total HDL cholesterol before and during hormonal intake, but no other statistically significant correlation between glycemic control (estimated by insulin requirement, fasting plasma glucose, 24-h blood glucose profile, and HbA_{1c}) and lipoproteins and lipids could be demonstrated.

Effect of tobacco smoking

The median values for age and duration of IDDM were similar in the women who smoked ($n = 20$) and in the women who did not ($n = 22$). Among the variables given in Tables 1, 2, and 3, we found no differences of statistical significance between the baseline values for the smokers and the nonsmokers. Within the treatment group, we observed the same influence of hormonal intake on lipids and lipoproteins in the smokers ($n = 11$) as in the nonsmokers ($n = 11$).

CONCLUSIONS— When the prescription of oral contraceptives to women with IDDM is considered, the benefits of the optimal fertility control provided by the pills should be correlated to their pos-

Table 3—*Serum levels of lipids and lipoproteins before and during 12 months of observation of 20 women with IDDM*

Variable	Baseline	1 month	3 months	6 months	12 months
n	20	20	20	19	19
Total cholesterol (mmol/l)	5.40 (3.46–7.08)	5.23 (4.07–8.42)	5.14 (4.28–8.03)	5.27 (4.05–7.56)	5.06 (3.77–7.45)†
LDL cholesterol (mmol/l)	3.27 (1.47–5.11)	3.24 (1.71–6.46)	3.23 (2.01–5.21)	3.14 (1.79–5.71)	2.86 (1.81–4.71)*
HDL cholesterol (mmol/l)	1.64 (1.08–2.33)	1.70 (0.88–2.20)	1.76 (0.89–2.20)	1.67 (0.99–2.13)	1.85 (0.88–2.75)†
HDL_2 cholesterol (mmol/l)	0.86 (0.17–1.23)	0.84 (0.07–1.37)	0.83 (0.08–1.57)	0.92 (0.17–1.39)	0.88 (0.11–1.95)†
HDL_3 cholesterol (mmol/l)	0.83 (0.67–1.13)	0.84 (0.59–1.13)	0.83 (0.63–1.11)	0.82 (0.69–1.15)	0.94 (0.70–1.30)*
HDL cholesterol/total cholesterol	0.31 (0.17–0.49)	0.32 (0.16–0.49)	0.33 (0.16–0.46)	0.31 (0.14–0.50)	0.35 (0.17–0.59)*
VLDL cholesterol (mmol/l)	0.44 (0.26–0.84)	0.43 (0.19–0.83)	0.40 (0.22–1.00)	0.42 (0.29–1.10)	0.43 (0.29–1.16)†
Triglycerides (mmol/l)	0.96 (0.56–1.83)	0.92 (0.41–1.81)	0.87 (0.47–2.18)	0.92 (0.64–2.39)	0.94 (0.64–2.51)†
Apolipoprotein A (g/l)	1.35 (1.05–1.92)	1.43 (0.92–1.69)	1.41 (0.78–1.71)	1.30 (1.10–1.78)	1.45 (1.05–1.72)†
Apolipoprotein B (g/l)	1.00 (0.32–1.40)	0.93 (0.56–1.95)	0.92 (0.57–1.44)	0.92 (0.59–1.55)	0.84 (0.61–1.42)†

Data are medians (range). This table includes data that have been published separately on total cholesterol, HDL and LDL cholesterol, and triglycerides for 12 women (9). * Baseline values vs. treatment values: $P < 0.05$. † Baseline values vs. treatment values: NS.

sible impairment of diabetic control and their effects on metabolic variables involved in the development of late complications of diabetes. In this study, we found no indications of impaired glycometabolic control during 1 year of intake of oral contraceptives containing ethinyl estradiol and gestodene and no effects on lipoprotein metabolism known to promote atherosclerotic disease were observed.

Our study may, however, be unable to detect small but relevant changes in metabolic variables because of the high risk of type 2 error that is a consequence of the limited number of women participating in the study (13). This is illustrated by the fact that we would need 227 women in the oral contraception group to detect a difference of 1.7 mmol/l between baseline and treatment values of fasting plasma glucose when accepting a type 1 error of 5% and a type 2 error of 10%. On the other hand, the limited number of patients reduces the possibility that the differences actually observed have occurred by chance.

The hormonal treatment was well tolerated by the participants. The continuation rate and the reasons for stopping treatment were similar to observations made in nondiabetic women participating in similar trials in the same setting (6). Clinically significant influence of the hormonal treatment on diabetic control was, however, observed in one woman, who experienced increased frequency and severity of hypoglycemic attacks during treatment despite unchanged insulin dosage, physical activity, and diet. Her glycemic control was restored after cessation of hormonal treatment. Similar side effects have not previously been described in women with IDDM using oral contraceptives, but earlier studies reported a significant increase in the insulin requirements during intake of other oral contraceptives containing different progestogens and a generally higher estrogen content than the compound tested in our study (5,14). In contrast with these observations, we found no indications of impaired diabetic control; unchanged values of fasting plasma glucose, 24 h-blood glucose profile, HbA_{1c}, daily insulin requirement, and plasma levels of free fatty acids were noted throughout the study period. The present combination of ethinyl estradiol and gestodene has not previously been evaluated in diabetic women, but studies on preparations with similar estrogen content combined with levonorgestrel or norethindrone have also failed to detect impairment of glycemic control (15).

In nondiabetic women, intake of oral contraceptives may induce changes in plasma lipoprotein composition similar to those found in patients with poorly regulated diabetes, i.e., hypertriglyceridemia and elevated levels of total and LDL cholesterol (16,17). These changes have been linked to the increased risk of vascular disease among oral contraceptive users indicated in epidemiological studies (17). The influence on lipids and lipoproteins of different oral contraceptives depends on the dose of the estrogen component and the type and dose of the progestogen used, and recent studies have shown that the compound tested in the present study exerts only minor effects on lipoprotein metabolism in nondiabetic women (6,18).

The majority of the participants in our study had baseline values of lipids and lipoproteins within the normal range for nondiabetic subjects, and the medians of the baseline values were not different from those previously reported in nondiabetic women of similar age (6). Moreover, we found similar effects of hormonal intake on serum levels of lipids and lipoproteins in women with diabetes to those previously reported in nondiabetic women (6,18), a relationship that has been described with other preparations as well (15). In the control group, however, we did observe a decrease in LDL cholesterol. The most obvious explanation for this change seems to be the intensified clinical control performed during the study period.

We found no correlation between lipids and lipoproteins and HbA_{1c} levels either before or during hormonal intake, so we could not confirm earlier findings of this covariation (19); this may be due to the small number of women with high HbA_{1c} levels in our study. These findings may indicate that the effect of exogenous sex steroids on the mechanisms regulating the serum concentration of lipids and lipoproteins in circulation is not different in women with diabetes. It must, however, be considered that changes in the biological properties of the lipoproteins caused by altered glycosylation, a process that cannot be evaluated with conventional quantitative laboratory analysis, may be present in diabetic patients (20,21).

Our finding of unchanged levels of HbA_{1c} indicated that hormonal intake was not associated with increased glycosylation of proteins, and qualitative changes of the lipoproteins caused by glycosylation are therefore unlikely to have occurred. It does, however, remain to be determined whether the steroids are able to modify the metabolism of lipoprotein particles inside the diabetic vessel wall, as indicated in animal models (22).

The general, as well as the vascular, morbidity in patients with IDDM who smoke is greater than that expected from the combined effect of the two factors (23), and smoking seems to be an independent risk factor for the development of microalbuminuria in patients with diabetes (24). In addition, smoking may be associated with unfavorable serum levels of lipoproteins in patients with diabetes (25) and has also been reported to influence oxidation of the LDL particle, thereby enhancing its atherogenic properties (26). The combined action of smoking and oral contraceptive use on lipids and lipoproteins has not previously been studied in diabetic women. However, our findings suggest that tobacco smoking does not influence the baseline serum values of lipids and lipoproteins and the response to hormonal intake seems to be similar in smokers and nonsmokers. It must, nevertheless, be considered that only light smokers (<10 cigarettes/day)

<35 years of age and without vascular complications were included in this evaluation.

In conclusion, intake of oral contraceptives containing ethinyl estradiol and gestodene for 12 months did not interfere with diabetic control, and no effects on serum levels of lipoproteins associated with the development of atherosclerosis were observed. We found a similar response to hormonal treatment in smokers and in nonsmokers. Experimental evidence of functional alterations of lipoproteins caused by the metabolic disturbance of diabetes itself and possibly enhanced by tobacco smoking may, however, suggest that oral contraception should not be the contraceptive method of choice for diabetic women who smoke. Studies on the effects of steroids on lipoprotein metabolism in the diabetic artery wall are needed to evaluate their possible effect on the accelerated atherosclerotic process that is characteristic of this disease.

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References

1. Hanson U, Persson B, Thunell S: Relation between hemoglobin A1c in early type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortions and fetal malformation in Sweden. *Diabetologia* 33:100–104, 1990
2. Mills JL, Simpson JL, Driscoll SG, Jovanovic-Peterson L, van Allen M, Aarons JH, Metzger B, Bieber FR, Knopp RH, Holmes LB, Peterson CM, Withiam-Wilson M, Brown Z, Ober C, Harley E, Macpherson TA, Duckles A, Mueller-Heubach E, the National Institute of Child Health and Human Development–Diabetes in Early Pregnancy Study: Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. *N Engl J Med* 319:1617–1623, 1988
3. Kjer K, Hagen C, Sandø SH, Eshøj O: Contraception in women with IDDM: an epidemiological study. *Diabetes Care* 15: 585–590, 1992
4. Steel JM, Duncan LJP: Serious complications of oral contraceptives in insulin-dependent diabetes. *Contraception* 17: 291–295, 1978
5. Rådberg T, Gustafson Å, Skryten A, Karlsson K: Oral contraception in diabetic women: diabetes control and high density lipoprotein lipids during low dosage progestogen, combined oestrogen/progestogen and non-hormonal contraception. *Acta Endocrinol* 98:246–251, 1981
6. Petersen KR, Skouby SO, Pedersen RG: Desogestrel and gestodene in oral contraceptives: 12 months assessment of glucose and lipoprotein metabolism. *Obstet Gynecol* 78:666–672, 1991
7. White P: Pregnancy and diabetes: medical aspects. *Med Clin North Am* 49:1015–1024, 1965
8. Petersen KR, Skouby SO, Sidelmann J, Jespersen J: Assessment of endothelial function in women with insulin-dependent diabetes mellitus during oral contraception. *Metabolism* 43:1379–1383, 1994
9. Petersen KR, Sidelmann J, Skouby SO, Mølsted-Pedersen L, Jespersen J: Effects of contraceptive steroids on cardiovascular risk factors in women with insulin-dependent diabetes mellitus. *Am J Obstet Gynecol* 171:400–405, 1994
10. Dolhofer R, Weiss L, Wieland OH: Experience with the glucose-dehydrogenase-UV-method for the determination of blood glucose. *J Clin Chem Clin Biochem* 14:415–417, 1976
11. Jones SL, Close CF, Mattock MB, Jarrett, Keen H, Viberti GC: Plasma lipid and coagulation factor concentration in insulin-dependent diabetics with microalbuminuria. *Br Med J* 298:487–490, 1989
12. Talameh Y, Wei R, Naito H: Measurement of total HDL, HDL_2 and HDL_3 by dextran sulfate-$MgCl_2$ precipitation technique in human serum. *Clin Chim Acta* 158:33–41, 1986
13. Freimann JA, Chalmers TC, Smith H, Kuebler RR: The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 299:690–694, 1978
14. Steel JM, Duncan LJP: The effects of oral contraceptives on insulin requirement in diabetics. *Br J Fam Plann* 3:77–78, 1978
15. Skouby SO, Mølsted-Pedersen L, Kuhl C, Bennet P: Oral contraceptives in diabetic women: metabolic effects of four compounds with different estrogen/progestogen profiles. *Fertil Steril* 46:858–864, 1986
16. Taskinen MB: Quantitative and qualitative lipoprotein abnormalities in diabetes mellitus. *Diabetes* 41 (Suppl. 2):12–17, 1992
17. La Rosa JC: The varying effects of progestins on lipid levels and cardiovascular disease. *Am J Obstet Gynecol* 158:1621–1629, 1988
18. Gevers Leuven JA, Dersjant-Roorda MC, Helmerhorst FM, de Boer R, Neymeyer-Leloux A, Havecs I: Estrogenic effect of gestodene- or desogestrel-containing oral contraceptives on lipoprotein metabolism. *Am J Obstet Gynecol* 163:358–362, 1990
19. Ostlund RE, Semenkovich CF, Schechtman KB: Quantitative relationship between plasma lipids and glycohemoglobin in type I diabetes. *Diabetes Care* 12: 332–336, 1989
20. Witztum JL, Mahoney EM, Branks MJ, Fisher M, Elam R: Steinberg D: Nonenzymatic glycosylation of low-density lipoprotein alters its biological activity. *Diabetes* 31:283–291, 1982
21. Duell PB, Oram JF, Bierman EL: Nonenzymatic glycosylation of HDL and impaired HDL receptor mediated cholesterol efflux. *Diabetes* 40:377–384, 1991
22. Haarbo J, Leth-Espesen P, Stender S, Christiansen C: Estrogen monotherapy and combined estrogen-progestogen replacement therapy attenuate aortic accumulation of cholesterol in ovariectomized cholesterol-fed rabbits. *J Clin Invest* 87: 1274–1279, 1991
23. Gay EC, Cai Y, Gale SM, Baron A, Cruickshanks KJ, Kostraba JN, Hamman RF: Smokers with IDDM experience excess morbidity: the Colorado IDDM registry. *Diabetes Care* 15:947–952, 1992
24. Microalbuminuria Collaborative Study

Group: Risk factors for development of microalbuminuria in insulin-dependent diabetic patients. *Br Med J* 306:1235–1239, 1993

25. Dullaart RP, Groener JE, Dikkeschei BD, Erkelens DW, Doorenbos H: Elevated cholesteryl ester transfer protein activity in IDDM men who smoke: possible factor for unfavorable lipoprotein profile. *Diabetes Care* 14:338–341, 1991
26. Scheffler E, Wiest E, Woehrle J, Otto I, Schulz I, Huber L, Ziegler R, Dresel HA: Smoking influences the atherogenic potential of low-density protein. *Clin Invest* 70:263–268, 1992