Oral Contraceptive Use and Association With Glucose, Insulin, and Diabetes in Young Adult Women

The CARDIA Study

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OBJECTIVE — We studied the associations between *1*) current use of oral contraceptives (OCs) and *2*) glucose levels, insulin levels, and diabetes in young women.

RESEARCH DESIGN AND METHODS — Subjects were women (n = 1,940) in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a prospective observational study of African-Americans and whites aged 18–30 years at enrollment in 1985–1986. We analyzed the cross-sectional associations between *1*) current use of OCs and *2*) fasting glucose, fasting insulin, and presence of diabetes using generalized estimating equations to adjust for repeated measures. We also examined the effect of current use of OCs on incident diabetes at year 10 of the study.

RESULTS — In unadjusted analyses, current use was associated with lower fasting glucose levels [–3.1 mg/dl, 95% CI (−3.7, –2.5)] and reduction in the odds of diabetes [odds ratio 0.56 (0.32, 0.97)], but not lower fasting insulin levels [−0.01 μU/ml (−0.03, 0.02)], compared with nonuse in both African-American and white women. After adjustment for covariates, current use of OCs was still associated with lower fasting glucose levels [–1.8 mg/dl (−2.4, –1.3)] and lower odds of diabetes [odds ratio 0.56 (0.33, 0.95)], although the associations were attenuated. After adjustment, current use of OCs was associated with higher insulin levels [0.12 μU/ml (0.006, 0.23)]. No association existed between pattern of use of OCs and incident diabetes at year 10, although the total number of new persons with diabetes at year 10 was small (n = 17).

CONCLUSIONS — Current use of OCs is associated with lower glucose levels in young African-American and white women and may be associated with lower odds of diabetes.

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Given the increasing incidence of type 2 diabetes in the U.S. among young minority women (1,2), it is important to understand the association between combination oral contraceptives (OCs) and glucose intolerance in this population. Combination estrogen-progestin OCs are used by more than 10 million women in the U.S. (3), and most studies indicate that they are associated with increased glucose and insulin levels (4–7).

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Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; OC, oral contraceptive.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

However, the association has been inconsistent. This inconsistency is possibly explained by small numbers of participants and inability to evaluate and adjust for all potential confounders, such as increased BMI, age, nonwhite race, lower education level, family history of diabetes, or health behaviors. Also, studies that did not find an association did not specifically exclude persons with diabetes, and persons with diabetes may have taken OCs less often because of their disease (8,9).

Prospective cohort studies of both older high-dose estrogen-progestin formulations (10) and newer low-dose estrogen-progestin formulations (11) did not find an increased incidence of type 2 diabetes in current OC users or former OC users after adjustment for these factors. However, the populations studied had an older age at enrollment and were not adjusted for race. They were also unable to study fasting glucose or insulin levels and, therefore, the effect of use of OCs on concurrent glucose and insulin metabolism.

To determine whether use of OCs increased glucose and insulin levels and risk of diabetes, we studied the cross-sectional association between *1*) current use of OCs and *2*) glucose levels, insulin levels, and diabetes in a population of 1,940 young African-American and white women participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study. We also examined the longitudinal association between current use of OCs and incident diabetes at year 10. Extensive data were collected on possible confounders.

RESEARCH DESIGN AND METHODS

Study population

The CARDIA study is a prospective cohort study designed to identify determinants of the evolution of cardiovascular risk factors in young adults. The study design and characteristics of the cohort

have been described (12). Briefly, young adults aged 18–30 years, half of whom were African-American or women, were recruited in 1985–1986 from four geographic locations by community-based sampling (Birmingham, AL; Chicago, IL; Minneapolis, MN) or through the membership of a large prepaid health care plan (Oakland, CA); 5,115 individuals participated in baseline examinations, including 2,787 women, and retention of the surviving female cohort at year 10 was 78% (n = 2,180). Questionnaires, examinations, and blood tests were also performed at years 2, 5, 7, and 10 of the study; serum glucose and insulin levels were obtained at examination years 0, 7, and 10. All female participants (n = 2,787) were eligible for the present analysis unless they were pregnant at the time of the baseline, year 7, or year 10 examinations (n = 93) or if they missed any of the examinations at baseline, year 7, or year 10 (n = 751). Women were also excluded if they did not have contraceptive, glucose, or insulin levels available for any of the examinations (n = 3), but they were included if they had this information for any of the examinations. Women who did not attend all three examinations were younger and were more likely to be African-American and have fewer years of education, lower physical activity scores, and higher smoking rates at baseline than those who did attend.

Data collection

For this study, women were grouped into two categories of use at each examination: current users and nonusers. Current use was defined as use of OCs at the time of each examination, and nonuse was defined as other categories of use. Former use and never use were combined into current "nonuse," because preliminary analysis of the year 10 data showed no significant difference between these groups for the covariates listed in Table 1 as well as no difference in the end points of glucose levels, insulin levels, and diabetes. In addition, previous studies have found that after cessation of OCs, risk of diabetes quickly diminishes to that found among women who have never used OCs; also, duration of use within the former and current categories was not related to diabetes (11). Formulations of OCs were combined due to small numbers of women reporting use of specific types. At year 10, 90% of participants used formu-

Table 1—*Means (SE) or percentages for selected measures at years 0, 7, and 10 by current use of OCs*

	Year 0			Year 7			Year 10		
Measure	Not Current	Current	*P* value	Not current	Current	*P* value	Not current	Current	*P* value
N	1,318	606		1,527	409		1,633	287	
Age (years)	25.5 (0.1)	24.3 (0.1)	<0.0001	32.6 (0.1)	30.5 (0.2)	<0.0001	35.4 (0.1)	33.6 (0.2)	<0.0001
Race (% African-American)	47.9	56.4	<0.0001	51.4	47.4	0.15	52.1	40.1	<0.0001
Education (years)	13.9 (0.1)	14.0 (0.1)	0.62	14.5 (0.1)	15.0 (0.1)	<0.0001	14.6 (0.1)	15.3 (0.1)	<0.0001
Number of pregnancies	1.2 (0.0)	0.9 (0.1)	0.0015	2.0 (0.0)	1.4 (0.1)	<0.0001	2.3 (0.0)	1.4 (0.1)	<0.0001
Family history of diabetes	18.0	17.0	0.55	24.3 (5)	19.4	0.042	29.9	26.7	0.27
BMI (kg/m^2)	24.9 (0.2)	24.1 (0.2)	0.0045	27.4 (0.2)	25.4 (0.3)	<0.0001	28.2 (0.2)	25.8 (0.4)	<0.0001
Waist-to-hip ratio	0.74 (0.002)	0.73 (0.002)	<0.0001	0.76 (0.002)	0.73 (0.003)	<0.0001	0.76 (0.002)	0.74 (0.004)	<0.0001
Alcohol (ml ethanol/day)	7.1 (0.4)	7.4 (0.5)	0.69	6.3 (0.3)	5.6 (0.5)	0.32	6.5 (0.4)	6.3 (0.7)	0.76
Physical activity score*	291 (154,483)	284 (154,476)	0.53	204 (95,372)	220 (107,408)	0.13	196 (85,356)	227 (112,428)	0.008
Current smoker (%)	34.8	33.0	0.42	26.8	19.1	0.002	24.7	15.4	<0.0001
Currently married (%)	25.5	23.3	0.29	44.0	42.4	0.58	47.3	47.7	0.90
Mean arterial pressure (mmHg)	80.1 (0.2)	80.2 (0.3)	0.92	80.2 (0.3)	79.8 (0.4)	0.52	82.9 (0.3)	82.5 (0.5)	0.52
HDL (mg/dl)	55.7 (0.4)	56.4 (0.5)	0.33	54.8 (0.4)	57.6 (0.7)	0.0002	53.5 (0.3)	56.9 (0.9)	0.0002
Triglyceride (mg/dl)*	52 (30)	69 (36)	<0.0001	56 (38)	73 (44.5)	<0.0001	62 (44)	78 (54)	<0.0001

Data are means (SE) or %. *Median and interquartile range presented; rank-sum test used for comparison.

Table 2—*Regression coefficients and odds ratios (95% CIs) for dependent variables (fasting glucose, fasting insulin, diabetes, and hyperinsulinemia)*

	Fasting glucose (mg/dl)	Diabetes*	Fasting insulin (μU/ml)†
Unadjusted	−3.1 (−3.7, −2.5)	0.56 (0.32, 0.97)	−0.01 (−0.03, 0.02)
Adjusted for covariates‡	−1.7 (−2.3, −1.1)	0.64 (0.39, 1.1)	0.15 (0.02, 0.27)
Adjusted for covariates above and BMI (kg/m^2)	−1.3 (−1.9, −0.76)	0.65 (0.39, 1.1)	0.15 (0.04, 0.26)
Adjusted for covariates above and HDL cholesterol (mg/dl) and triglyceride levels (mg/dl) and mean arterial pressure (mmHg)	−1.8 (−2.4, −1.3)	0.56 (0.33, 0.95)	0.12 (0.01, 0.23)

*Diabetes defined by self-report. Reference group is non-current oral contraceptive use. Participants with diabetes excluded from analyses except for "diabetes" analyses. †Regression coefficient reported with log of fasting insulin; ‡covariates are age (years), race, education (years), number of pregnancies, family history of diabetes, alcohol consumption (ml/day), smoking (current, not current), and physical activity.

lations that contained <50 μg of ethinyl estradiol, and the most commonly used formulation was Ortho-Novum 1/35 (18% of participants); formulations containing >50 μg of estrogen totaled <4%, and formulations containing the newer progestins desogestrel or norgestimate totaled <13%; progestin-only formulations totaled <5%. For years 0, 7, and 10 combined, most women used first-generation OCs: only 10% used second-generation OCs, and only 2% used third-generation OCs.

Age, race, and education were collected by interview at all examinations. Family history of diabetes by self-report was collected at baseline and at the 5- and 10-year examinations; the family history of diabetes at year 7 was assumed to be the same as the family history of diabetes at year 5. Family history of diabetes was defined as at least one first-degree relative with diabetes. Measurement of alcohol intake (13), physical activity (14), height, weight, and calculation of BMI and waist-to-hip ratio (15) have been previously described. Cigarette smoking status was obtained by self-report at each examination (16).

Venous blood samples were collected in EDTA at each of the field centers according to a common protocol. Fasting insulin was measured by a radioimmunoassay using an overnight, equilibrium incubation and using a unique antibody that had <0.2% cross-reactivity to human proinsulin and its primary circulating split form Des 21,32 proinsulin 36. Blind analysis of split serum samples yielded a technical error of 16.6% of the mean and $r = 0.98$. Fasting glucose was measured using the hexokinase method at each examination but was collected at years 0 and 7 in standard red-top Vacutainer tubes and at year 10 in Vacutainer tubes containing a glycolytic inhibitor (iodoacetic acid) (17). Women were excluded from analyses of glucose and insulin levels if they had not fasted for at least 8 h before the venipuncture at the year 0, 7, or 10 examinations (37, 150, and 94 participants, respectively).

For this report, we used two definitions of diabetes: *1*) diabetes by self-report (24, 111, and 127 participants at years 0, 7, and 10, respectively) and *2*) diabetes by use of diabetes medication or fasting glucose ≥126 mg/dl (15, 20, and 38 participants, at years 0, 7, and 10, respectively). The question ascertaining diabetes did not distinguish between type 1 and type 2. At baseline, all participants in this analysis taking diabetes medication took insulin; at year 7, 11 of the 15 participants taking diabetes medication took insulin, and at year 10, 14 of the 20 participants taking diabetes medication took insulin.

Statistical analysis

Primary analyses focused on the cross-sectional associations between use of OCs and glucose, insulin, and diabetes at the year 0, 7, and 10 examinations. Cross-sectional analysis was performed to examine the association of use of OCs on concurrent glucose and insulin metabolism and to avoid misclassification of use of OCs, as OC status was collected at several points in time. First, we compared current users and nonusers within each examination for the variables listed in Table 1 with Student's *t* tests or rank-sum tests for the continuous variables and χ^2 or Fisher's exact tests for the categorical variables. The relationship between current use of OCs at each examination and glucose and insulin levels and diabetes at the same examination was assessed using linear and logistic regression. Individuals with diabetes were excluded from analyses of glucose and insulin but included in analyses of diabetes.

Next, we performed cross-sectional analysis of the relationship between current use of OCs and these end points, combining the results from the three examinations (Table 2). Because outcome variables were repeated and not independent measures within individuals over time, we used generalized estimating equations (GEE). Insulin and physical activity were log-transformed; although alcohol intake was also skewed, log transformation did not improve the distribution (18). The models presented in the cross-sectional analysis adjusted for variables in several stages, first by demographic covariates (age, race, education, parity, family history of diabetes) and behavioral covariates (alcohol consumption, current smoking status, physical activity) and then for BMI, blood pressure, and cholesterol measures. The models were also run excluding patients taking medications for diabetes, blood pressure, or lipid reduction. We repeated the analysis stratifying by race, BMI strata, and quartiles of waist-to-hip ratio. These covariates were chosen based on recognized or potential associations between these factors and risk of diabetes.

Finally, we analyzed the longitudinal association between current use of OCs and diabetes by comparing incident diabetes at year 10 between different patterns of OC use. The rate of incident diabetes was examined for women who did not use OCs at any examination year, women who used OCs at baseline but not thereafter, women who used OCs at baseline and at year 7 but not at year 10, and women who used OCs at all three exam-

ination years. All calculations were performed using STATA Statistical Software (19).

RESULTS

Participant characteristics

At all examinations, current OC users were younger and had fewer pregnancies, lower mean BMI, lower waist-to-hip ratios, lower current smoking rates, and more years of education (Table 1). Initially, current users were more likely to be African-American, but by year 10, they were more likely to be white. By year 10, current users were more likely to be more physically active. The percentage of women using OCs decreased as the cohort aged.

Current use of OCs and glucose, insulin, and diabetes at each examination year

The unadjusted association between current use of OCs and fasting glucose and insulin levels and diabetes by self-report at each examination year was examined. Individuals with diabetes were excluded from the analyses of glucose and insulin but were examined in the analysis of diabetes. Compared with noncurrent OC use, current OC use was significantly associated with lower unadjusted fasting glucose levels at year 0 (78.6 vs. 81.2 mg/dl, $P < 0.0001$), year 7 (84.2 vs. 86.7 mg/dl, $P < 0.0001$), and year 10 (82.3 vs. 85.3 mg/dl, $P < 0.0001$). Similarly, current use of OCs was associated with a significantly lower percentage of individuals with diabetes at year 0 (0.3 vs. 1.7%, $P = 0.014$), year 7 (3.7 vs. 6.3%, $P = 0.043$), and year 10 (2.8 vs. 7.2%, $P = 0.005$). Current use of OCs was associated with slightly higher insulin levels at year 0 (12.1 vs. 11.7 μU/ml, $P = 0.0068$) but not at year 7 (12.8 vs. 14.2 μU/ml, $P = 0.51$) and by year 10 was associated with slightly lower insulin levels (12.0 vs. 13.7 μU/ml, $P = 0.01$). When we defined diabetes by glucose or medication use instead of by self-report, the association between diabetes and current OC use persisted, except that the association between current use of OCs and diabetes was no longer significant at years 0 and 7 due to the small number of individuals with diabetes.

Current use of OCs and glucose, insulin, and diabetes, pooled examinations

The unadjusted cross-sectional association between current OC use and these end points, obtained by combining the data from the 3 exam years, is shown in Table 2. Persons with diabetes were excluded from the analyses of glucose and insulin but examined in the analysis of diabetes. Current use of OCs was associated with lower concurrent fasting glucose levels but was not associated with lower concurrent fasting insulin levels. Current use of OCs was also associated with a lower unadjusted odds of diabetes by self-report and hyperinsulinemia. These associations were similar when diabetes was defined by glucose level or medication use instead of by self-report.

The adjusted cross-sectional association between current use of OCs and these end points from the combined data are also shown in Table 2. The cross-sectional association between current use of OCs and fasting insulin levels changed with the addition of covariates, so that current use of OCs was associated with elevated fasting insulin levels. Adjusting for all covariates, including mean arterial pressure, HDL levels, and triglyceride levels, resulted in statistically significant associations between current use of OCs and decreased fasting glucose, current use of OCs and decreased odds of diabetes, and current use of OCs and increased insulin levels. The results did not change significantly when an interaction term between race and BMI or between age and OC was introduced into the model. Excluding participants taking medication for diabetes, blood pressure, or lipid reduction or stratification by BMI and waist-to-hip ratio did not reveal any significant differences (results not shown).

Analysis of African-Americans and whites separately did not reveal significant differences between races. Therefore, results in African-Americans are similar to those reported in Table 2, although CIs widened due to reduced sample size. In African-American women, current use of OCs was associated with lower fasting glucose levels in unadjusted analyses [–3.9 mg/dl, 95% CI (−4.9, −3.0)] and after adjustment for all covariates listed in Table 2 [–0.88 mg/dl (−1.9, 0.18)]. Similarly, in African-American women, current use of OCs was associated with lower odds of diabetes before adjustment [odds ratio 0.62 (0.31, 1.2)] and after adjustment for all covariates above [odds ratio 0.50 (0.22, 1.1)]. Finally, current OC use was inconsistently associated with log fasting insulin levels from before adjustment [−0.03 μU/ml (−0.07, 0.01) to after adjustment [0.01 μU/ml, 95% CI (−0.04, 0.05)] for all covariates above.

Incident diabetes

Finally, when we examined the longitudinal relationship between OC use and incident diabetes, we were limited by the number of new cases of diabetes by glucose levels and medication use at year 10 ($n = 17$) and the new cases of diabetes by self-report at year 10 ($n = 37$). The predominant pattern of use of OCs was no use at years 0, 7, or 10 ($n = 907$, 56%); roughly 2% of this group had a new diagnosis of diabetes at year 10. There was no significant association between incident diabetes at year 10 and a particular pattern of oral contraceptive use, whether we defined diabetes by self-report ($P = 0.28$) or by medication and glucose level ($P = 0.59$).

CONCLUSIONS — We found that current use of OCs was associated with lower glucose levels in a racially diverse sample of young women. Current use of OCs had an inconsistent association with insulin levels, with no association before adjustment but an association with higher insulin levels after adjustment for covariates. In cross-sectional analysis, current use of OCs was associated with a lower odds of diabetes. The association between use of OCs and incident diabetes was not significant in longitudinal analysis, although the number of women with incident diabetes at year 10 was low. To our knowledge, this analysis of current use of OCs and glucose levels, insulin levels, and diabetes involves the largest numbers of young African-American women to date. In the face of a type 2 diabetes epidemic, which disproportionately affects minorities and increasingly affects young women, the possibility that use of OCs may be associated with a lower odds of diabetes may have important clinical implications, although this finding must be replicated. Also, our results on glucose and insulin levels are somewhat reassuring, especially because previous analyses of current use of OCs and glucose and insulin levels have found either no significant association (8,9) or an association

with higher levels of glucose (20,21) and insulin (21).

In the Bogalusa Heart Study (9), current use of OCs was not related to glucose or insulin levels in a cross-sectional analysis. However, the study was only able to adjust for age and subscapular skin thickness, and individuals with diabetes were not explicitly excluded. In a cross-sectional analysis of the Cardiovascular Risk in Young Finns study, Porkka et al. (8) did not find a significant association between current use of OCs and insulin levels in women, although individuals with diabetes were not explicitly excluded.

Other studies of OCs found that current use of combination OCs was associated with significantly higher glucose levels (20,21) and insulin responses (21) compared with nonuse. Our results may have differed because of our ability to adjust for additional variables. It is also possible that our study subjects included a larger proportion of women with polycystic ovary disease, as CARDIA participants were more obese; in women with polycystic ovary disease, OCs may suppress follicle-stimulating hormone and luteinizing hormone, in turn suppressing ovarian androgen secretion and thereby decreasing insulin resistance and glucose levels (22).

Estrogen may lead to decreased fasting glucose levels by depressing hepatic glucose production (23); estrogen may act as a glucagon antagonist by increasing the molar ratio of insulin to glucagon in the hepatic portal vein, reducing the basal activity of phosphoenol pyruvate carboxykinase, the key gluconeogenic enzyme (24). In postmenopausal women, estrogen replacement has been linked with decreased hyperandrogenicity and improved glucose homeostasis (25,26). The association between OCs and insulin has been less consistent, perhaps partially due to increased variability in insulin levels (27). OCs have been associated with insulin resistance during intravenous glucose tolerance testing (28), determined primarily by estrogen effect and not associated with progestagenicity and androgenicity. However, the association between OCs and fasting insulin is believed to depend largely on the dose and type of progestogen, with hyperinsulinemic responses most evident with levonorgestrel (23) and less common with norethindrone or desogestrel (5,6). Few of the women in our study were using OCs containing levonorgestrel at year 10, but it is possible that women may have had different responses to OCs depending on their insulin levels before initiation of OCs; a trial of hormone replacement in postmenopausal women has found that insulin and glucose effects were most pronounced among women who had elevated levels of pretreatment fasting insulin and postprandial glucose (26). It is possible that women in our study had higher fasting insulin levels, which in turn may have been associated with increased 2-h glucose levels, but were also associated with decreased fasting glucose through hepatic glucose suppression.

When we examined the cross-sectional association between current use of OCs and the presence of diabetes, current use of OCs seemed to be related to lower diabetes risk in both African-American and white women, although CIs were wide. Prospective analyses of the Nurses Health Study, a population that was predominantly white and older at enrollment, found no association between current use of OCs and incident diabetes or former use of OCs and incident diabetes after adjustment for multiple covariates and after analysis by formulation (10,11). Our contradictory findings may be partially explained by our different study design; we examined concurrent diagnosis of diabetes rather than incident diagnosis. It is possible that patients with the diagnosis of diabetes were prescribed OCs less often than individuals without diabetes, but we excluded persons with diabetes from the analysis of glucose levels and still found a negative association between use of OCs and fasting glucose levels. Although possible surveillance bias may have existed in our analysis (i.e., current OC users underwent more frequent screening for diabetes), this should have biased the association in the other direction.

There are several limitations that must be considered in interpreting our findings. Our study is primarily cross-sectional, and it is unknown whether OCs were avoided in women with diabetes or whether OC use itself influenced glucose and diabetes development. However, we were concerned with the effect of OC use on concurrent glucose and insulin levels, and longitudinal analyses may have been limited by misclassification of OC status. Information on side effects of OCs was not collected, and it is possible that side effects would occur in women more likely to develop glucose tolerance. Because women in the CARDIA study primarily used first-generation OCs, we were unable to assess for the effect of different types of progestins; as previously mentioned, second-generation progestins may be associated with a higher risk than third-generation progestins (5,6,29). We were unable to assess whether patients had type 1 or type 2 diabetes; this is an unpredictable source of bias but may explain the failure to find a relationship between use of OCs and incident diabetes at year 10. Another unpredictable source of bias is that women with endocrinopathies, e.g., polycystic ovary disease, were less likely to take OCs due to infertility but more likely to take OCs because of menstrual irregularities. We were unable to adjust for a diagnosis of gestational diabetes. It is possible that patients with this diagnosis would have been prescribed OCs less often but are also more likely to develop diabetes, although the importance of birth control is believed to outweigh the diabetogenic potential of OCs (30). Furthermore, gestational diabetes may be a precursor of type 2 diabetes, and therefore adjustment would have falsely lowered the association between OCs and glucose levels. Finally, it is possible that other unmeasured confounders affect use of OCs and also affect development of diabetes.

In conclusion, current use of OCs does not seem to be associated with impaired carbohydrate metabolism or increased risk of diabetes in young women. On the contrary, OCs are associated with significantly lower glucose levels and may be associated with lower odds of diabetes in young African-American and white women. OCs may be associated with higher insulin levels, but the effect on glucose levels is difficult to ascertain.

Although the relative influence of OCs on diabetes risk may be significantly less than that of other risk factors, use of OCs represents a modifiable exposure with the significant health benefit of birth control. The association between lower glucose levels and OCs could be important, as women develop diabetes at a progressively younger age. In addition, although the findings on diabetes must be replicated, the potential significance is large considering the numbers of women using OCs and the increasing incidence of type 2 diabetes. Further examination of the physiology of OCs and carbohydrate metabolism could explain the inconsis-

tent association between OCs and insulin. Future analyses could focus on the influence of OCs in groups of women at high risk for glucose intolerance, such as those with endocrinopathies.

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