A Prospective Study of Oral Contraceptives and NIDDM Among U.S. Women

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OBJECTIVE — To examine prospectively the association between modern oral contraceptives with low doses of estrogen and progestin and subsequent incidence of NIDDM.

RESEARCH DESIGN AND METHODS — In a prospective cohort study, 98,590 U.S. female nurses aged 25 to 42 and free of diagnosed diabetes, coronary heart disease, stroke, and cancer at baseline in 1989 were followed for 4 years. Endpoint was incidence of confirmed NIDDM. Oral contraceptive use was reported on mailed questionnaires.

RESULTS — During 352,067 person-years of follow-up, we confirmed 185 incident cases of NIDDM. After adjusting for age, BMI, cigarette smoking, family history of diabetes, parity, physical activity, alcohol intake, ethnicity, history of diagnosis of infertility, elevated cholesterol, and hypertension, women currently using oral contraceptives had a relative risk (RR) of 1.6 (95% CI, 0.9–3.1). For past users, the multivariate RR was 1.2 (95% CI, 0.8–1.8). This association was attenuated after restricting the analysis to symptomatic cases of NIDDM. For current users, RR = 1.3 (95% CI, 0.6–2.8), and for past users, RR = 0.9 (95% CI, 0.6–1.4), suggesting that increased surveillance may explain at least part of any excess risk.

CONCLUSIONS — In this large prospective study, we found no appreciable increase in the 4-year risk of NIDDM among current users of oral contraceptives. There was no apparent increase in risk among past users. The small number of cases reflect the low absolute risk of NIDDM in this population of young women.

Current users of oral contraceptives have been reported to experience about twice the risk of impaired glucose tolerance compared to nonusers, and the increased risk appears to be related to both the dosage and formulation of the oral contraceptive (1). In studies of women taking the older, high-dose oral contraceptives (containing at least 50 mcg estrogen and 1–4 mg progestin), those at increased risk of impaired glucose tolerance had a positive family history of diabetes, had previous gestational diabetes, were obese, or were older than 40 years of age (2–6). Low-dose oral contraceptives with a reduced content of estrogen and progestin as well as the triphasic oral contraceptives are associated with a significantly lower excess risk of impaired glucose tolerance (7).

However, the long-term effects of low-dose oral contraceptives on the development of NIDDM remain relatively unexplored. Because the first oral contraceptives containing lower doses of estrogen combined with low doses of progestins were introduced in the mid-1970s and became widely used in the 1980s, epidemiological data with sufficiently long follow-up to examine the relationship between these current formulations and risk of NIDDM are sparse. Previous studies have provided summary estimates of risk across both users of high- and users of low-dose pills, have lacked information on potential confounding factors, and have had inadequate power to examine the effects of the individual steroid preparations (2,8).

We studied the relationship between modern oral contraceptives with low doses of estrogen and progestin and incidence of NIDDM prospectively among the 116,686 participants in the Nurses' Health Study II aged 25 to 42 years when enrolled in 1989. These younger women have predominantly used the modern low-dose formulations. The prevalence of NIDDM has been estimated to be 2.0% for women aged 20 to 44 years (9). Although this prevalence is low, diabetes is a major contributor to cardiovascular events. The Nurses' Health Study I found that although diabetic women constituted only 2% of the total study population aged 30–55 years in 1976, an estimated 13.8% of coronary events, 12.1% of ischemic strokes, and 14.8% of cardiovascular deaths were attributable to diabetes (10).

RESEARCH DESIGN AND METHODS

— The Nurses' Health Study II is an ongoing prospective cohort study designed to examine the association between lifestyle and nutritional factors and the occurrence of breast cancer and other major illnesses. In 1989, 116,686 female registered nurses 25–42 years of age who were living in one of 14 U.S. states responded to a baseline questionnaire. Follow-up questionnaires were sent in 1991 and 1993, with response rates of 93 and 92%, respectively.

We excluded from analysis women who reported a diagnosis of diabetes (n = 1,003), gestational diabetes (n = 3,353), cancer (except nonmelanoma skin cancer) (n = 1,046), myocardial infarction (n = 574), or stroke (n = 321) before 1989, the start of the follow-up period. Women who had not had a physical examination in the 2 years prior to the baseline questionnaire (n =

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RR, relative risk.

12,584) were excluded to avoid a potential bias due to the greater opportunity for diabetes diagnosis among oral contraceptive users as they may undergo routine urine screens or other regular testing. One or more of the exclusion criteria were met by 18,096 of the participants, leaving 98,590 eligible nurses who were followed for incidence of NIDDM in the subsequent 4 years. At the beginning of the second 2-year follow-up period (1991–1993), we excluded women who reported a diagnosis of the above diseases since 1989 (n = 1169) as these women may have altered their oral contraceptive use due to their illness.

Measurement of oral contraceptive use and other exposure variables

A complete history of oral contraceptive use was obtained at baseline in 1989. For each year from age 13 to age at baseline, duration of oral contraceptive use in 2 categories (2–<10 months, 10+ months–full year) was recorded. Less than 2 months of oral contraceptive use was counted as nonuse. We also provided a booklet with photos, names, and the pharmacological contents of the 227 oral contraceptives ever marketed in the U.S. up to the time of the study. This detailed list included separate codes for 21- vs. 28-day pills with the same pharmacological preparation and dose, for changes in packaging of the same preparation and dose, and for different pharmacological preparations or doses sold under the same brand name. For each age at which an oral contraceptive was used for at least 2 months, we asked the nurses to indicate from the booklet which brand was used (if multiple brands were used during that year of age, the brand used the longest). Information about subsequent use and brand of oral contraceptives was obtained from the next biennial follow-up questionnaire. We calculated the duration of each reported interval and then summed all of the intervals from both the baseline and follow-up questionnaire to ascertain duration of current and past use. We used the information on brand to categorize oral contraceptive use in terms of: type, dose, and biological potency of estrogen and progestin and formulation (monophasic, biphasic, and triphasic combination, or progestin only). We examined the relationship between these variables and risk of NIDDM in both current and past oral contraceptive users.

Validation of oral contraceptive use

We assessed the validity of self-report of oral contraceptive history by conducting a telephone interview among 215 randomly selected participants at least 8 months after completion of the baseline questionnaire (Hunter et al., personal communication, 1996). The interview used reproductive and other life events as cues for recall of contraceptive history. Of 177 nurses who reported by telephone interview that they had ever used oral contraceptives, 175 (99%) had reported this on the baseline questionnaire. Of 38 never-users by telephone interview, 37 (97%) reported never use on the baseline questionnaire. Mean duration of use among ever users was similar by questionnaire (mean = 54.8 months, standard deviation = 41.0) and telephone interview (mean = 51.8 months, standard deviation = 40.6), with a correlation of 0.94. For a subset of women for whom we were able to obtain oral contraceptive prescription records, the medical record confirmed the use of an identical or equivalent brand in 74% of intervals of reported use. However, this percentage is most likely an underestimate since women may receive prescriptions for different brands from more than one source, or may change brands or prescribers during an interval of use.

Diagnosis of NIDDM

We mailed a supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy to nurses who responded positively on any follow-up questionnaire to the question, "Have you been physician-diagnosed with diabetes?" The supplementary questionnaire was mailed in 1991 to women reporting diabetes newly diagnosed between 1989 and 1991 and subsequently in 1993 to women reporting diabetes between 1991 and 1993. A case of diabetes was considered confirmed if at least one of the following was reported on the supplementary questionnaire: *1*) one or more classic symptoms (thirst, polyuria, weight loss, hunger, pruritis) plus fasting plasma glucose at least 140 mg/dl (7.8 mmol/l) or random plasma glucose at least 200 mg/dl (11.1 mmol/l); 2) at least two elevated plasma glucose concentrations on different occasions (fasting at least 140 mg/dl and/or random at least 200 mg/dl and/or concentration at least 200 mg/dl after 2 or more hours on oral glucose tolerance testing) in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). Only a few confirmed cases were based on oral glucose tolerance tests or medication use alone (1.7 and 1.0%, respectively). Of the confirmed cases, 74% reported ever receiving hypoglycemic medication. We excluded women with IDDM, which was defined as confirmed diabetes and *1*) continuous insulin therapy begun within 1 year of diabetes diagnosis, plus 2) ketonuria (more than trace) on at least two occasions or hospitalization for ketoacidosis. In addition, we excluded 3,435 women classified as having gestational diabetes only. The remaining women with confirmed diabetes (n = 185) were classified as having NIDDM and form the basis for these analyses. Criteria for the classification of diabetes have been published in detail elsewhere (11).

Self-reported diagnosis of NIDDM was validated using these National Diabetes Data Group criteria (12) in the Nurses' Health Study I (11), a complementary cohort of 121,700 female nurses aged 30–55 years in 1976. The validity of diagnosis based on the supplementary questionnaire was confirmed in 61 of 62 women (98%) for whom medical records were obtained.

Statistical analysis

Women accumulated person-time of follow-up until the date of diabetes, cancer, heart disease diagnosis, or June 1, 1993, whichever came first. Rates of NIDDM were obtained by dividing the number of cases by person-years in each category of oral contraceptive use. Rate ratios were computed as the rate of occurrence of NIDDM in each category of oral contraceptive use divided by the incidence rate in the never users. We used proportional hazard models (13) to control simultaneously for potential confounders: BMI (kg/m^2) in deciles, age in 5-year intervals, alcohol intake, physical activity, ethnic group, cigarette smoking, parity, family history of diabetes, history of diagnosis of elevated cholesterol, history of diagnosis of hypertension, and 2-year time periods (see footnote of Table 2 for categories of covariates). We also controlled for history of diagnosis of infertility as there is evidence that the gene(s) determining NIDDM is associated with diminished fertility (14). Time-varying covariates (age, BMI, cigarette smoking, parity, physical activity, alcohol intake) were reassigned after 2 years according to the updated exposure values reported on the 1991 follow-up questionnaire. Because oral contraceptive users undergo regular screenings at least every year that may include routine urine screens and other tests, they may be more

Table 1—*Baseline characteristics according to oral contraceptive status among 98,590 U.S. women, 25–42 years of age, free from cardiovascular disease and diabetes in 1989*

Characteristic	Oral contraceptive status		
	Never	Past	Current
Number in 1989	15,851	69,160	13,579
Mean age (years)	34.2	34.3	33.9
BMI (kg/m^2)	24.1	23.7	23.1
Family history of diabetes (%)	18	16	16
Alcohol (g/day)	2.2	3.0	3.7
Physical activity (METs/week)	23	22	24
History of infertility (%)	15	21	11
History of hypertension (%)	6	6	4
History of elevated cholesterol (%)	9	11	11
Duration of oral contraceptive use (years)	—	3.9	8.1

All characteristics are standardized to the age distribution of the entire population. A family history of diabetes is defined as a mother, father, or sibling with diagnosed diabetes. MET score is defined as the metabolic equivalent of sitting at rest for 1 h for an adult of average weight.

likely to be diagnosed with NIDDM in the absence of symptoms than are nonusers of oral contraceptives. We therefore repeated these analyses only among the symptomatic cases of NIDDM (report of at least one symptom at diagnosis, including thirst, polyuria, weight loss, hunger, or pruritis).

Obesity, family history of diabetes, and age were strong predictors of NIDDM in this population; we therefore analyzed risk associated with category of oral contraceptive use within categories of BMI, family history, and 5-year age intervals.

We calculated the 95% CI for each rate ratio (15). Tests of trend across categories of oral contraceptive use were calculated by including a single trend variable coded as the category of exposure (1, 2, etc.) (16). We calculated risk differences by subtracting the age-adjusted incidence rate for never users from the corresponding rate in each category of oral contraceptive use. The population attributable risk was calculated using the formula given by Miettinen (17). All *P* values are two-tailed.

RESULTS — In 1989, 82,739 (84%) women reported past or current use of oral contraceptives (Table 1). Compared with women who never used oral contraceptives, current users were of similar age but were slightly leaner, had a higher alcohol intake, and were less likely to have a family history of diabetes, a previous diagnosis of infertility, or a history of hypertension. Women who were past users were similar to current users, although they had a slightly lower alcohol intake and were more likely to have been diagnosed with infertility.

During 352,067 person-years of follow-up, we confirmed 185 incident cases of NIDDM. The 4-year cumulative incidence of NIDDM ranged from 0.04% for women 25–29 years of age to 0.44% for women 45 years and older. After adjusting for age, neither current nor past users of oral contraceptives had an appreciably increased risk of NIDDM compared with women who never used oral contraceptives (Table 2). After further adjustment for BMI, cigarette smoking, family history of diabetes, parity, physical activity, alcohol intake, ethnicity, history of infertility, history of elevated cholesterol, and history of hypertension, current users had an RR of NIDDM of 1.6 (95% CI, 0.9–3.1) and past users an RR of 1.2 (95% CI, 0.8–1.8) as compared with never users. Confounding by obesity was largely responsible for the increase in the RR for current users in the multivariate model. Oral contraceptive users tended to be slightly leaner, and obesity increases risk of NIDDM. Thus, a portion of the observed lack of effect in the age-adjusted model is masked by this leanness. After controlling for BMI, the RR for oral contraceptives and NIDDM became higher.

Users of oral contraceptives may be more closely monitored by their physicians than nonusers of oral contraceptives and therefore may be more likely to be screened for diabetes. To reduce detection bias, we calculated RRs using only incident symptomatic cases of diabetes (n = 140). As compared with never users, the multivariate RR of NIDDM was attenuated to 1.3 (95% CI, 0.6–2.8) among current users and to 0.9 (95% CI, 0.6–1.4) among past users (Table 2). As there were only 11 symptomatic cases among the current users, the CIs were quite wide.

We investigated the association between duration of oral contraceptive use and NIDDM among both past and current users. There was no increase in risk with increasing duration of past use (P_{trend} = 0.19). The multivariate RR for NIDDM among those with <2 years of past use was

Table 2—*RRs of NIDDM among never, past, and current users of oral contraceptives*

NIDDM	Oral contraceptive status		
	Never	Past	Current
All cases			
Cases	31	139	15
Person-years	54,443	255,100	42,524
Age-adjusted RR (95% CI)*	1.0 (referent)	0.9 (0.6–1.3)	1.0 (0.5–1.8)
Age- and obesity-adjusted RR (95% CI)†	1.0	1.0 (0.7–1.5)	1.5 (0.8–2.8)
Multivariate RR (95% CI)‡	1.0	1.2 (0.8–1.8)	1.6 (0.9–3.1)
Symptomatic cases only			
Cases	28	101	11
Age-adjusted RR (95% CI)	1.0 (referent)	0.7 (0.5–1.0)	0.8 (0.4–1.6)
Age- and obesity-adjusted RR (95% CI)	1.0	0.8 (0.5–1.2)	1.2 (0.6–2.5)
Multivariate RR (95% CI)	1.0	0.9 (0.6–1.4)	1.3 (0.6–2.8)

Data are from 352,067 person-years of follow-up between 1989 and 1993 among 98,590 women from the Nurses' Health Study II. *Controlling for 5-year age categories.†Controlling for 5-year age categories and deciles of BMI (kg/m^2). For multivariate RR, multivariate model includes age (25–29, 30–34, 35–39, 40–44, ≥45), BMI (deciles), cigarette smoking (never, past, 1–14, 15–24, 25–34, 35+ cigarettes per day), family history of diabetes, parity (nulliparous, 1–2, 3–4, 5+ pregnancies), physical activity (quintiles), alcohol (g/day; none, 0.1–<1.5, 1.5–<5.0, 5.0–<15.0, 15+), ethnicity (Caucasian, African-American, Hispanic, Asian, missing), history of diagnosis of infertility (no, yes), history of diagnosis of elevated cholesterol (no, yes), and history of diagnosis of hypertension (no, yes). For symptomatic cases, symptoms at diagnosis included at least one of the following: thirst, polyuria, weight loss, hunger, or pruritis.

Table 3—*RRs of NIDDM according to duration of current oral contraceptive use*

NIDDM	Duration of current oral contraceptive use		
	Never (referent)	<6 Years	6+ Years
All Cases			
Cases	31	5	10
Person-years	54,443	18,722	23,660
Age-adjusted RR (95% CI)	1.0 (referent)	0.8 (0.3–2.3)	1.1 (0.5–2.3)
Age- and BMI-adjusted RR (95% CI)*	1.0	1.2 (0.5–3.1)	1.7 (0.8–3.5)
Multivariate RR (95% CI)†	1.0	1.3 (0.5–3.4)	1.9 (0.9–3.9)
Symptomatic cases only‡			
Cases	23	2	9
Age-adjusted RR (95% CI)	1.0 (referent)	0.3 (0.1–1.5)	1.1 (0.5–2.3)
Age- and BMI-adjusted RR (95% CI)	1.0	0.5 (0.1–2.3)	1.7 (0.8–3.6)
Multivariate RR (95% CI)	1.0	0.6 (0.1–2.5)	1.9 (0.9–4.0)

Data are from 352,067 person-years of follow-up between 1989 and 1993 among 98,590 women from the Nurses' Health Study II. *Controlling for 5-year age categories and 10 categories of BMI (kg/m²). †For multivariate RR, multivariate model includes age (25–29, 30–34, 35–39, 40–44, ≥45), BMI (deciles), cigarette smoking (never, past, 1–14, 15–24, 25–34, 35+ cigarettes per day), family history of diabetes, parity (nulliparous, 1–2, 3–4, 5+ pregnancies), physical activity (quintiles), alcohol (g/day; none, 0.1–<1.5, 1.5–<5.0, 5.0–<15.0, 15+), ethnicity (Caucasian, African-American, Hispanic, Asian, missing), history of diagnosis of infertility (no, yes), history of diagnosis of elevated cholesterol (no, yes), and history of diagnosis of hypertension (no, yes). ‡For symptomatic cases, symptoms at diagnosis included at least one of the following: thirst, polyuria, weight loss, hunger, or pruritis. Note: Current users with missing information on duration of use (142 person-years) were not included in this table.

1.5 (95% CI, 0.9–2.3); for 2 to <4 years, the RR was 1.2 (95% CI, 0.7–2.0); for 4 to <6 years, the RR was 0.6 (95% CI, 0.3–1.2); and for 6 years or more, the RR was 1.1 (95% CI, 0.7–1.8).

Women who had currently used oral contraceptives for relatively long periods of time appeared to be at greater risk of NIDDM than were short-term users. Compared with never users, current users with less than 6 years of oral contraceptive use had a multivariate RR of 1.3 (95% CI, 0.5–3.4), and those with 6 years or more of use had a multivariate RR of 1.9 (95% CI, 0.9–3.9) (Table 3). However, the test for trend over increasing categories of current use was not statistically significant (P_{trend} = 0.24). As in all of our analyses, we adjusted for age in 5-year categories.

Oral contraceptive use may increase the risk of NIDDM through acute serum glucose elevation. If so, one would expect to find no evidence for an effect of past use, even if use was recently terminated. On the other hand, if the effect were chronic, one would expect a gradual decline of risk toward baseline values with increasing time since last use. We categorized time since last use into four categories and found no decrease in risk with increasing time since last use, consistent with an acute effect (P_{trend} = 0.52). The multivariate RR for NIDDM among those with <2 years since last oral contraceptive use was 0.8 (95% CI, 0.3–1.8); for 2 to <4 years, the RR was 1.0 (95% CI, 0.4–2.3); for 4 to <6 years, the RR was 0.8 (95% CI, 0.3–2.0); and for 6 years or more, the RR was 1.3 (95% CI, 0.8–1.9).

Obesity, family history of diabetes, and age were all strongly associated with NIDDM in this population. Compared with women with no family history, the age-adjusted RR for women with a positive family history of diabetes was 1.6 (95% CI, 1.2–2.2). The RR of NIDDM among women aged 35–39 years was 4.0 (95% CI, 2.0–7.8) compared with women aged 25–29. Women with a BMI of 24 to <27 kg/m² had an RR of 9.5 (95% CI, 1.8–49.5) compared with women in the lowest quintile (<20 kg/m²). We analyzed differences in risk within categories of these variables and found that the association between oral contraceptive use and risk of NIDDM did not vary appreciably (Table 4).

We further examined oral contraceptives by type of formulation: monophasic combination, biphasic combination, triphasic combination, and progestin-only pills. Compared with never users, current users both of triphasic and of monophasic combination oral contraceptives had a modest but statistically nonsignificant increased risk of NIDDM. For users of monophasics, the multivariate RR was 1.7 (95% CI, 0.7–4.0); for users of triphasics, the multivariate RR was 1.8 (95% CI, 0.7–5.0). There were too few users of progestin-only or biphasic oral contraceptives to estimate risk. The small number of cases in the category of current users (n = 15) precluded more detailed analyses of biological potency and risk of NIDDM; however, most women were taking combination oral contraceptives with low estrogenic and progestational potency.

CONCLUSIONS — In this large prospective study among U.S. women, we found no appreciable increase in risk of NIDDM among current users of oral contraceptives compared with never users after adjustment for age, BMI, and other lifestyle factors. There was a suggestion, although not statistically significant, of increased risk among those currently using oral contraceptives for the longest durations. The small number of cases of NIDDM reflect the low risk of NIDDM in this cohort of young women.

Oral contraceptive users may be more likely than nonusers to visit their physicians and therefore may be more likely to be diagnosed with preclinical diabetes than would a nonuser with the same occult condition. If surveillance bias were present, it would inflate the RR among users. To address this concern, we restricted all the analyses only to nurses who reported having had a physical exam within the 2 years prior to the baseline questionnaire. When we further restricted the cases to those with symptoms only, the increased risk among current users was attenuated from 1.6 to 1.3, which suggests that surveillance bias may have played a role.

Increased knowledge among health professionals of the effects of oral contraceptives has led to better selection of potential oral contraceptive users on the basis of medical history and better supervision of users during follow-up. Although we controlled for many of the medical history factors that could influence prescription (family history of diabetes, BMI, parity, diagnosis of hypertension, elevated cholesterol, and infertility), this selectivity could partially account for the low risks that we observed.

We validated self-report of diabetes in this population through a detailed supplementary questionnaire but did not obtain medical records. The excellent ability of a complementary cohort of female nurses to self-report the diagnosis of diabetes as shown by medical record review suggests the validity of self-reported diagnosis by

Table 4—*Multivariate RRs and 95% CIs of NIDDM by BMI, family history of diabetes, and age at baseline among never, past, and current users of oral contraceptives*

	Cases	Person-years	Oral contraceptive use		
			Never	Past	Current
BMI (kg/m²)					
<27.0 (CI)	25	268,076	1.0 (referent)	0.6 (0.2–1.7)	1.2 (0.3–5.1)
≥27.0 (CI)	151	63,137	1.0	1.3 (0.8–2.0)	1.2 (0.6–2.7)
Family history					
Yes (CI)	88	56,860	1.0 (referent)	1.0 (0.6–1.7)	1.5 (0.6–3.8)
No (CI)	97	295,207	1.0	1.4 (0.8–2.6)	1.7 (0.7–4.2)
Age					
25–29 years	8	51,687	1.0 (referent)	1.2 (0.2–7.2)	3.6 (0.7–19.4)
30–34 years	33	106,678	1.0	1.2 (0.5–2.8)	1.0 (0.3–3.3)
35–39 years	72	117,606	1.0	1.3 (0.7–2.5)	1.2 (0.3–4.5)
≥40 years	72	76,095	1.0	1.1 (0.5–2.2)	3.3 (0.7–16.0)

Data are from 352,067 person-years of follow-up between 1989 and 1993 among women from the Nurses' Health Study II. Variables are added to the model independently. Multivariate model includes age (25–29, 30–34, 35–39, 40–44, ≥45), BMI (deciles), cigarette smoking (never, past, 1–14, 15–24, 25–34, 35+ cigarettes per day), family history of diabetes, parity (nulliparous, 1–2, 3–4, 5+ pregnancies), physical activity (quintiles), alcohol (g/day; none, 0.1–<1.5, 1.5–<5.0, 5.0–<15.0, 15+), ethnicity (Caucasian, African-American, Hispanic, Asian, missing), history of diagnosis of infertility (no, yes), history of diagnosis of elevated cholesterol (no, yes), history of diagnosis of hypertension (no, yes). Women with missing information on BMI (20,854 person-years and 9 cases) were not included in the analysis by category of BMI. A family history of diabetes is defined as a mother, father, or sibling with diagnosed diabetes. For BMI, test for heterogeneity, $P = 0.11$; for family history, test for heterogeneity, $P = 0.78$; for age, test for heterogeneity, $P = 0.74$.

nurses in this cohort. The prospective design of the study eliminates any bias associated with differential recall of oral contraceptive use. As nurses were free from NIDDM in 1989 when they reported their oral contraceptive history, recall of oral contraceptive use was not influenced by diagnosis of diabetes.

No firm clinical conclusion has yet been made on the diabetogenic potential of oral contraceptives (7). However, the ability of high-dose oral contraceptives to impair glucose tolerance has been widely acknowledged. The second National Health and Nutrition Examination Survey (NHANES II), conducted in the U.S. from 1976 to 1980, found impaired glucose tolerance in 15.4% of current oral contraceptive users as opposed to 6.3% in nonusers (6). Similarly, the Walnut Creek Contraceptive Drug Study, a 10-year prospective follow-up of the health effects of oral contraceptives, observed impaired glucose tolerance in 16% of current users via a 2-h glucose tolerance test versus an 8% prevalence in nonusers (18).

Previous literature has suggested that among high-dose oral contraceptive users, those at risk of NIDDM are those at risk of this condition in general. These include women with a positive family history of diabetes, previous gestational diabetes, or who are obese or older (1,7). In a prospective study of this association, Rimm et al. (19) followed 115,117 women for 12 years and found no increased risk of NIDDM among current users of oral contraceptives (RR = 0.86; 95% CI, 0.46–1.61) compared with women who had never used the drug, regardless of category of BMI or family history of diabetes. However, that study included both users of high- and users of low-dose oral contraceptives. Family history, age, and obesity did not modify the relationship between oral contraceptives and NIDDM in our cohort of predominantly low-dose users.

We found no difference in risk according to time since last oral contraceptive use. Among those women with less than 4 years since last oral contraceptive use, the multivariate RR was 0.9 (95% CI, 0.4–1.7). This is consistent with reports that impaired glucose tolerance returns to normal within 6 to 12 months after cessation of oral contraceptives (1,5,20,21). Those who discontinued oral contraceptives 6 or more years ago had no discernible higher risk than those stopping more recently (RR = 1.3; 95% CI, 0.8–1.9). Six years or more is a time after which the transitory effect of oral contraceptives on glucose tolerance would long have ended (22).

Our population of nurses was young (less than 50 years of age) and followed for 4 years. Since risk of NIDDM increases with age, it is possible that, with additional follow-up, perturbation in glucose tolerance related to oral contraceptive use could have a greater impact on risk of NIDDM in an older population or among those who are already at increased risk for NIDDM. Similarly, current oral contraceptive use could have a greater impact on risk of NIDDM in particular ethnic groups who generally have an early age of NIDDM onset.

Our population of users of the predominantly modern low-dose oral contraceptive formulations had no appreciable increase in risk of NIDDM. The small number of cases in our cohort reflect the low absolute risk of NIDDM in this population of young women. The findings would predict only 2 excess cases of NIDDM per 100,000 person-years of current use. After cessation of oral contraceptives, risk quickly diminishes to that found among women who have never used oral contraceptives. Thus, this study suggests that risk of diabetes should not be a major concern when prescribing low-dose oral contraceptives.

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