

Contraception and the Risk of Type 2 Diabetes Mellitus in Latina Women With Prior Gestational Diabetes Mellitus

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Context.—Effective contraception is essential in women with prior gestational diabetes mellitus (GDM) but should not increase their already substantial risk of developing type 2 diabetes.

Objective.—To determine whether exposure to low-dose oral contraceptives increases the risk of developing type 2 diabetes mellitus in women with recent GDM.

Design.—Retrospective cohort study of 904 Latinas with GDM who gave birth between January 1987 and March 1994, in whom postpartum diabetes was excluded at 4 to 16 weeks post partum.

Interventions.—At their initial postpartum visit, 443 women selected a nonhormonal form of contraception, 383 received a low-dose, estrogen-progestin combination oral contraceptive (OC), and 78 breast-feeding women received the progestin-only OC. When breast-feeding ended, patients initially taking progestin-only OCs were switched to combination OCs. Patients were followed up periodically with oral glucose tolerance tests for up to 7½ years.

Main Outcome Measures.—Person time was used to compute unadjusted average annual incidence rates of developing diabetes mellitus, as defined by the National Diabetes Data Group Criteria. Survival analysis was used to compute the unadjusted cumulative incidence rates and adjusted relative risks of diabetes mellitus.

Results.—The unadjusted average annual incidence rates of type 2 diabetes mellitus were 8.7%, 10.4%, and 26.5%, respectively, for patients using nonhormonal forms of contraception, combination OCs, and progestin-only OCs. Cumulative incidence rates were virtually identical for patients with uninterrupted use of combination OCs and nonhormonal forms of contraception, but patients using progestin-only OCs developed diabetes mellitus more rapidly during the first 2 years of use. After adjustment for potential confounding factors, the use of progestin-only OCs almost tripled the risk of type 2 diabetes mellitus compared with equivalent use of low-dose combination OCs (adjusted relative risk, 2.87; 95% confidence interval, 1.57-5.27). The magnitude of this risk increased with duration of uninterrupted use.

Conclusion.—Progestin-only OCs were associated with an increased risk of diabetes in breast-feeding Latinas with recent GDM and probably should be prescribed with caution, if at all, in these women. Long-term use of low-dose combination OCs did not increase the risk of type 2 diabetes compared with use of nonhormonal contraception. Thus, combination OCs do not appear to increase the risk of diabetes in non-breast-feeding women with recent GDM.

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ORAL CONTRACEPTIVES (OCs) are available in the United States in 2 general forms: progestin-only and combination estrogen-progestin OCs. While the metabolic effects of individual preparations vary, the impact of currently available progestin-only and low-dose combi-

nation OCs on glucose tolerance in the general population has been minimal.¹⁻⁶ Therefore, low-dose OCs are generally prescribed without concern about precipitation of hyperglycemia, and clinical monitoring of glucose levels is not recommended in healthy women.

Although the safety of low-dose hormonal contraception in the general population is reassuring, it is not clear that this safety profile applies to all patient groups. One group at increased risk of type 2 diabetes mellitus that is of particular interest is women with a recent history of gestational diabetes mellitus (GDM).^{7,8} We have reported that these women incur a 3-fold increase in their already high risk of developing diabetes if they complete an additional pregnancy after their initial diagnosis of GDM.⁹ Moreover, if they conceive after developing diabetes, they will place their newborns at increased risk of major congenital malformations.¹⁰ Clearly, women with a history of GDM need access to safe and effective contraception. Studies of OC use in women with a history of GDM have failed to identify a clear deleterious effect on circulating glucose levels.¹¹⁻¹⁴ However, because these studies have been relatively small and of short duration, they have had limited power to detect a clinically important effect on diabetes risk. We conducted the present investigation to determine whether the use of low-dose OC, either progestin-only or progestin-estrogen combination formulations, was associated with any alteration in the risk of diabetes in a large cohort of Latinas with recent GDM who were attending a high-risk family planning clinic.

METHODS

Subjects

Study subjects consisted of women who were attending the High-Risk Family Planning Clinic (HRFPC) at Los An-

geles County Women and Children's Hospital because of a history of recent GDM. All women whose pregnancy is complicated by GDM at this hospital are advised to return to the HRFPC 4 to 6 weeks after delivery and then annually for a 75-g oral glucose tolerance test (OGTT), administered and interpreted according to the National Diabetes Data Group (NDDG) recommendations.¹⁵ Approximately 45% of eligible women return for postpartum glucose tolerance testing and, of these, approximately half return for at least 1 additional OGTT. Women who elect to use hormonal contraception are scheduled for an additional OGTT 3 to 6 months after beginning the medication. Women also return to the clinic for intercurrent medical problems, for change in method of contraception, and when using hormonal contraception, every 6 months for contraceptive refills. At each visit, in addition to contraceptive counseling, patients are advised to exercise daily and attain or maintain ideal body weight; however, no formal dietary or exercise program is used, and no data are collected regarding compliance with these recommendations. Approximately, 97% of the women attending the HRFPC after GDM have Spanish surnames and were born in Mexico or Central America.

The 904 women described in this article included all patients who (1) had GDM, according to NDDG criteria,¹⁵ and had given birth at the Los Angeles County and University of Southern California Women's Hospital, Los Angeles, between January 1, 1987, and March 29, 1994; (2) had a nondiabetic OGTT at their initial postpartum visit 4 to 16 weeks after delivery; and (3) returned for at least 1 additional OGTT while not pregnant before December 2, 1994. Thirty-nine patients elected to use a nonoral form of hormonal contraception (ie, progestin injections or implants) at their initial postpartum visits and were excluded from these analyses. Study subjects were followed up from their initial postpartum visits until their last clinic visits prior to December 2, 1994, or until they developed the study end point, diabetes as defined by the NDDG criteria.¹⁵

Selection of Contraception

Patients selected contraceptive methods in consultation with reproductive health clinicians under the supervision of a faculty gynecologist (S.L.K.) in the HRFPC. It is clinic policy to prescribe to non-breast-feeding patients who elect to use OCs 1 of 2 combinations of OCs containing low doses of progestin and estrogen—either the monophasic norethindrone preparation (0.40 mg of norethindrone and 35 µg of ethinyl estradiol) or

the triphasic levonorgestrel preparation (0.050-0.125 mg of levonorgestrel and 30-40 µg of ethinyl estradiol). However, a few non-breast-feeding patients were prescribed some other combination OC for at least part of their follow-up when they expressed a preference based on their prior experience. Patients who elected to use OCs while continuing to breast-feed were uniformly prescribed the progestin-only OC (0.35 mg of norethindrone) until they stopped breast-feeding, after which they were switched to 1 of the low-dose combination OCs.

Testing Procedures

Oral glucose tolerance tests were conducted on sitting patients after a 10- to 12-hour overnight fast. Patients were advised to eat 3 meals and a snack daily for 3 days before testing. Blood was obtained by venipuncture before and at 30, 60, 90, and 120 minutes after glucose ingestion and was placed into heparin-fluoride-containing tubes. Plasma was separated and assayed for glucose using a Beckman Glucose Analyzer CX4 (Beckman Instruments, Brea, Calif). Glucose tolerance was evaluated as a single continuous variable by integrating the total area under the glucose tolerance curve (glucose AUC) of the OGTTs and as a categorical variable by the NDDG criteria for normal or impaired glucose tolerance or type 2 diabetes.¹⁵ Fasting blood samples for serum lipid determination were drawn into tubes without anticoagulants and serum was separated after the blood was allowed to clot for 1 hour. Total serum cholesterol and triglyceride concentrations were measured by enzymatic hydrolysis and oxidation. High-density lipoprotein cholesterol (HDL-C) levels were determined by oxidation after removal of low-density cholesterol (LDL-C) and very low-density lipoprotein (VLDL) cholesterol by precipitation. Low-density lipoprotein cholesterol levels were calculated as follows: cholesterol - [HDL-C + triglycerides/5] when triglyceride levels were less than 4.5 mmol/L (400 mg/dL). Blood pressure was measured with an aneroid sphygmomanometer after patients had been sitting for at least 5 minutes. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressure. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Patients' weights between follow-up visits were estimated by linear interpolation from their weights measured at the clinic visits directly before and after the date in question. Change in weight was calculated as the interpolated weight for a given point in time minus the baseline

weight (ie, measured weight at the postpartum visit for the index pregnancy).

Months of using each method of contraception were determined by data collected at each OGTT visit. Women who became pregnant during follow-up were assumed to have used no method of contraception for the duration of these pregnancies.

Data Analysis

Data analysis focused on the comparison of 3 types of contraception: nonhormonal contraception, progestin-only OCs, and combination OCs. For each type of contraception, the overall average annual incidence rate of diabetes was calculated from total person-days of follow-up, including discontinuous follow-up and follow-up after switching to a different type of contraception.

Cumulative incidence rates and unadjusted relative risks (RRs) for the development of diabetes were computed by maximum likelihood methods for interval-censored survival data, which censored subjects whenever they stopped using their entry contraceptive or became pregnant. For these analyses (ie, cumulative incidence rates and unadjusted RRs), we developed a program for survival analysis of interval-censored event times using a parametric step-function baseline hazard and a proportional hazards model. These analyses assumed that (1) the incidence rate of diabetes for women using a given type of contraception was constant over each interval (with widths ranging from 3 months during the first year to 1 year after year 3) and (2) a proportional hazards model with constant RR for each of the 3 contraceptive groups. The likelihood contribution for a subject developing diabetes was then $S_i(t_{i0}) - S_i(t_{i1})$, where t_{i0} is the time of the last normal OGTT, t_{i1} is the time of the first abnormal OGTT, and $S_i(t)$ denotes the survival function, computed under the usual proportional hazards model. The likelihood contribution for a subject not developing diabetes by time t_i was the usual $S_i(t_i)$. Adjusted RRs for the development of type 2 diabetes were estimated by Cox proportional hazards regression analysis¹⁶ using all follow-up data but only from women who used progestin-only or combination OCs, since the frequencies of metabolic testing were, per protocol, similar in these 2 groups and more frequent than the testing of women using nonhormonal forms of contraception. Use of each type of contraception was treated as a yes or no, time-dependent variable so that subjects could be transferred into or out of a given type of contraception at exactly the time in the life table that use of the relevant form of contraception was

started or stopped. We also examined models that assumed lag times in the onset of OC effects of 1 to 6 months and that assumed similar washout periods after the cessation of OC use, but the best predictors of diabetes assumed that the OC effects began and ended with their actual dates of use. The assumption of proportional hazard for progestin-only vs combination OC use was tested by adding time interaction to the model; no significant violation of this proportional assumption was observed. In the Cox regression analyses, potential confounders were examined one at a time and, then, in combination. The 4 variables that were found to be independent predictors of diabetes in this data set were included in all final analyses. They are (1) insulin treatment during the index pregnancy, (2) the glucose AVC the baseline OGTT, (3) weight change after the baseline visit (time-dependent variable), and (4) completion of an additional pregnancy after the index pregnancy (time-dependent variable). Since subjects were permitted to switch from 1 method of contraception to another without censoring, these analyses were also adjusted for prior use of a combination OC, prior use of a progestin-only OC, and prior use of a nonhormonal method of contraception, all as ever or never time-dependent variables. Adjustment for 3 additionally known predictors of diabetes from the index pregnancy (gestational age at diagnosis of GDM, highest fasting glucose level during the index pregnancy, and glucose AUC from the diagnostic OGTT[®]) did not substantially change the point estimates of our adjusted RRs but reduced our statistical power, since these parameters were incomplete in approximately one third of our subjects. Therefore, there were no adjustments for these 3 variables in the final analyses. Additional variables, some of which were univariate predictors of diabetes, were not included in the final analyses because they were no longer predictive after adjustment for other potential confounders and because they did not substantively alter the RRs associated with OC use when added 1 at time to the final Cox model. These variables were maternal age, parity, BMI, total cholesterol level, LDL-C and HDL-C levels, total triglyceride levels, blood pressure, and fasting glucose level, all as measured at the baseline postpartum visit, and the time between the index delivery and the beginning of OC use.

The distributions of continuous variables were tested for normality. For variables with skewed distributions, analyses were conducted on both the original and log-transformed variables. Since ad-

justment for the log-transformed variables invariably failed to change the point estimate of the RR for progestin-only vs combination OCs, all continuous variables were kept in their original form. Demographic and clinical characteristics of subjects who initially elected to use different types of contraception were compared by *t* tests or χ^2 statistics, as appropriate. All reported tests of statistical significance are 2-sided.

RESULTS

At their baseline postpartum visits, 461 of our study subjects chose to use an OC and 443 chose a nonhormonal method of contraception. Of those electing to use an OC, 78 were given the progestin-only OC since they were breast-feeding at their baseline postpartum visits and planned to continue breast-feeding. Of those electing OCs but not breast-feeding, 277 were given monophasic norethindrone (Ovcon), and 106 were given the triphasic levonorgestrel (Triphasil). Twenty-nine patients were initially prescribed 5 low-dose OCs in the following combinations: 14 patients received Ortho Novum 7/7/7 (0.5-1.0 mg of norethindrone); 7 patients received ModiCon (0.5-1.0 mg of norethindrone); 4 patients received Ortho Novum 1/35 (1.0 mg of norethindrone); 3 patients received Loestrin 1/20 (1.0 mg of norethindrone); and one patient received Nordette (0.150 mg levonorgestrel). All these preparations contained low doses of ethinyl estradiol (20-40 μ g). A total of 140 subjects (15.5%) changed methods of contraception at some time during follow-up, including 28 (35.9%) of those who initially used progestin-only OCs.

Compared with women who chose a nonhormonal form of contraception at the baseline postpartum visit, combination OC users were significantly younger and had significantly lower parity, BMI, cholesterol levels, and blood pressure at their baseline visits; they also gained less weight during follow-up (Table 1). Women given the progestin-only OC had higher parity, BMI, and cholesterol levels and gained more weight than combination OC users. Both groups of OC users were less likely to have another pregnancy during follow-up and both groups had shorter intervals between follow-up OGTTs, especially during the first year of follow-up, compared with users of nonhormonal contraception (Table 1).

The median months of use of the initial contraceptive method was slightly, albeit significantly, less in women who started using combination OCs than in women who started using nonhormonal contraception (Table 1). Maximum months of use of the initial method were similar in the 2 groups. Both of these pa-

rameters were lowest in women who started using progestin-only contraception, presumably because use of that method was limited to the period of breast-feeding. Frequencies of glucose tolerance testing, assessed as the number of months separating baseline, first follow-up, and second follow-up OGTTs, were similar in the combination and progestin-only OC groups. Testing was less frequent in the women who began with nonhormonal contraception. Six months after starting therapy, 86% of patients prescribed combination OCs and 83% of those given progestin-only OCs had returned for the additional OGTT that was recommended as part of the management protocol.

Altogether, 169 of the 904 study subjects developed diabetes during follow-up, giving an overall average incidence rate of 9.9% per year. All subjects who developed diabetes had clinical characteristics of type 2 diabetes. When any OC was being used, the average annual incidence rate of type 2 diabetes was 11.7%, compared with 8.7% when nonhormonal forms of contraception were used. When progestin-only OCs were used, the rate was 2.5 times the rate observed during combination OC use (26.5% vs 10.4%). These unadjusted rates were based on total person-days of use, including discontinuous use.

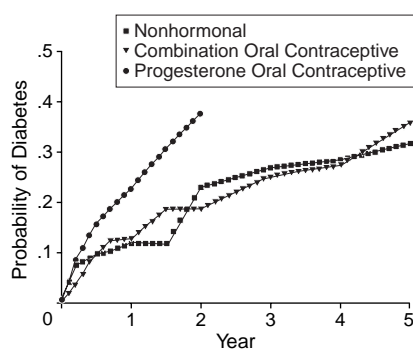
When only uninterrupted use of the same method of contraception was considered, the cumulative incidence rate of type 2 diabetes was also significantly greater among women taking progestin-only OCs than among either combination OC users ($P < .001$) or women who never used hormonal contraception ($P < .001$) (Figure). Women with uninterrupted use of combination OCs developed diabetes at roughly the same rate as those who had never taken OCs. The unadjusted summary RRs compared with those who had never used OCs and computed by interval-censored regression analysis were 1.07 (95% confidence interval [CI], 0.77-1.49) for combination OC users and 2.04 (95% CI, 1.46-2.70) for progestin-only OC users. The comparable unadjusted RR for progestin-only OC use vs combination OC use was 1.90 (95% CI, 1.39-2.58).

Proportional hazards regression analysis, using all follow-up information on all OC users, confirmed that, compared with the equivalent duration of use of combination OCs, the use of progestin-only OCs was associated with an increased risk of diabetes (Table 2). This risk persisted (adjusted RR, 2.87; 95% CI, 1.57-5.27) after adjusting for insulin treatment during the index pregnancy; the glucose AUC at the initial postpartum OGTT; weight change from the ini-

Table 1.—Characteristics According to Methods of Contraception at the Beginning of Follow-up*

Characteristics	Column 1 Nonhormonal (n=443)	Column 2 Combination Oral Contraceptive (n=383)	Column 3 Progestin-Only Oral Contraceptive (n=78)	Statistical Comparisons		
				P for Columns 1 vs 2	P for Columns 1 vs 3	P for Columns 2 vs 3
During index pregnancy						
Insulin treated, No. (%)	130 (29.4)	95 (24.8)	17 (21.8)	.14	.17	>.50
At postpartum visit						
Maternal age, y	31.3 (5.5)	28.5 (5.4)	29.4 (5.2)	<.001	<.01	.18
Parity	3.0 (1.8)	2.3 (1.2)	3.1 (1.8)	<.001	>.50	<.001
Body mass index, kg/m ²	29.6 (5.1)	28.2 (4.3)	29.4 (4.2)	<.001	>.50	<.05
Total cholesterol, mmol/L [mg/dL]	5.6 (1.1) [216.1 (43.3)]	6.4 (1.0) [207.6 (39.3)]	5.7 (1.2) [219.6 (44.5)]	<.01	>.50	<.05
Mean arterial pressure, mm Hg	84.5 (11.4)	82.5 (8.6)	82.2 (8.8)	<.001	.05	>.50
Fasting glucose, mmol/L [mg/dL]	5.2 (.65) [93.7 (11.7)]	5.1 (.65) [92.7 (11.7)]	5.1 (.61) [91.3 (11.1)]	.19	.09	.36
Glucose area under the curve, mg/min/1000 dL	16.7 (3.4)	16.4 (3.6)	16.8 (3.4)	.13	>.50	.27
Breast-feeding, No. (%)	183 (41.4)	0	78 (100)	<.001	<.001	<.001
During follow-up						
Became pregnant	18.1	6.3	3.9	<.001	<.001	>.05
Average weight change, kg [lb]	1.7 (5.4) [3.8 (12.0)]	0.5 (6.3) [1.1 (14.0)]	4.1 (10.8) [9.1 (23.9)]	<.01	.06	<.01
Median months using initial contraception	15.2	11.4	6.7	<.001	<.001	<.001
Maximum months using initial contraception	90.6	85.5	38.4
Months before first follow-up oral glucose tolerance test	14.6 (8.2)	6.9 (5.8)	7.0 (2.8)	<.001	<.001	>.50
Months between first and second follow-up oral glucose tolerance test	14.6 (6.2)	7.5 (3.5)	6.2 (2.4)	<.001	<.001	.18

*Values followed by numbers in parentheses are the mean (SD). Other values are the percentage, median, or maximum as stated. Body mass index is a measure of weight in kilograms divided by the square of height in meters. Ellipses indicates that no statistical analysis was performed on the maximum months of initial contraception.



Cumulative incidence rates of type 2 diabetes as determined by interval-censored survival analysis in 904 Latinas with recent gestational diabetes mellitus (GDM). The incidence of diabetes is depicted during the first 5 years after delivery for women who never used hormonal contraception, women who continuously used low-dose combinations oral contraceptives, and those who continuously used progestin-only oral contraceptives.

tial postpartum weight (time-dependent variable); completion of an additional pregnancy (time-dependent variable); and prior use of a combination OC, progestin-only OC, or a nonhormonal method (time-dependent variables). Furthermore, the risk of diabetes rose with increasing duration of progestin-only OC exposure (Table 2). Use for less than 4 months was not associated with a detectable increase in risk, but the CI around this estimate was wide. Periods of longer use was associated with a progressive increase in risk.

When OC exposure was limited to uninterrupted use of the initial OC and the

proportional hazards analysis was repeated, there was virtually no change in the estimated risk associated with progestin-only OCs (adjusted RR, 2.80; 95% CI, 1.52-5.15). Similarly, when we restricted our reference to the 2 low-dose combination OCs used most frequently (Ovcon 35 and Triphasil), there was little change in this summary risk estimate (adjusted RR, 2.43; 95% CI, 1.32-4.48). Lastly, when we restricted our reference to uninterrupted use of the most frequently prescribed combination OC (0.40 mg of norethindrone [Ovcon 35]), the adjusted RR associated with progestin-only OCs was 2.50 (95% CI, 1.33-4.71). The RR for the levonorgestrel-containing combination OC (Triphasil) was 1.12 (95% CI, 0.61-2.04).

Since progestin-only OC use was invariably associated with breast-feeding in this cohort, we looked for an independent effect of breast-feeding on the risk of developing diabetes among women who initially elected nonhormonal forms of contraception. Overall, 41% of these women were breast-feeding at the time of their initial postpartum examination and their risk of developing diabetes was not significantly different from the risk in women who elected nonhormonal contraception but did not breast-feed (unadjusted RR, 0.90; 95% CI, 0.56-1.46; adjusted RR, 1.16; 95% CI, 0.70-1.92).

COMMENT

The present article is, to our knowledge, the first large-scale investigation

of the impact of low-dose OCs on the risk of developing diabetes mellitus in women with prior GDM. The investigation revealed 2 important findings. First, the use of low-dose progestin and estrogen combination OCs did not appear to increase the risk of developing diabetes in these high-risk women. Second, the use of a progestin-only OC during breast-feeding was associated with a nearly 3-fold increase in the incidence of diabetes compared with the 2 other groups. This risk rose with increasing duration of uninterrupted OC use. Therefore, low-dose progestin and estrogen combination OCs appear safe for women already at high risk of developing diabetes, while the progestin-only OC appears to increase the risk of developing diabetes, at least while women breast-feed.

The increased risk of diabetes associated with use of norethindrone alone was somewhat surprising considering the lack of excess risk associated with combination OCs containing similar amounts of norethindrone or another progestational agent, levonorgestrel. Although our study does not provide a definitive explanation for these findings, examination of the different circumstances under which combination and progestin-only OCs were used may provide some clues. The progestin-only preparation was administered exclusively during breast-feeding, a time when endogenous estrogen levels are generally low and prolactin levels are elevated compared with those of non-breast-feeding, premenopausal women.¹⁷⁻¹⁹ An unop-

Table 2.—Relative Risks of Type 2 Diabetes Associated With Oral Contraceptive (OC) Use*

	No Adjustments Relative Risk† (95% Confidence Interval)	Adjusted Relative Risk† (95% Confidence Interval)
Use of progestin-only OC	2.58 (1.42-4.66)	2.87 (1.57-5.27)
Duration of uninterrupted use, mo‡		
≤4	0.71 (0.09-5.75)	0.72 (0.09-5.89)
4-8	2.62 (1.20-5.69)	2.96 (1.35-6.52)
>8	4.23 (1.56-11.43)	4.92 (1.76-13.73)

*The use of progestin-only OCs compared with low-dose, estrogen-progestin combination OCs in a follow-up investigation among women (n=461) with prior gestational diabetes, estimated by Cox proportional hazards regression analysis, using all follow-up on all OC users and combination OC use as the reference. All OC variables were modeled as "yes or no" time-dependent variables.

†Adjusted for insulin treatment during the index pregnancy, area under the glucose curve at baseline, weight change after baseline (time-dependent variable), completion of a second pregnancy (time-dependent variable), and prior OC use (time-dependent variable) when subjects became pregnant or switched from the type of OC initially prescribed for them.

‡All 3 "Duration of uninterrupted use" variables were modeled simultaneously as time-dependent variables.

posed or dominant progestational effect would be expected under these circumstances.²⁰ By contrast, non-breast-feeding women used low-dose progestin and estrogen combination OCs, which are estrogen dominant in their metabolic effect on carbohydrate and lipid metabolism.²¹ Studies of the relative effects of progestins and estrogens on carbohydrate metabolism indicate that the progestin component appears to induce insulin resistance in a dose- and potency-dependent fashion.²⁰⁻²² Estrogens, on the other hand, either have no effect on insulin sensitivity or glucose tolerance²³ or may actually enhance insulin action in vitro²⁴ and in vivo.²⁵ Estrogens also have been reported to have beneficial effects on pancreatic β -cell function in animal models of diabetes.²⁶ Taken together, these facts suggest that when estrogen levels are low (eg, during breastfeeding), progestational agents may well exert a more pronounced effect on induction of insulin resistance and deterioration in glucose tolerance. Conversely, the coadministration of estrogen should mitigate the diabetogenic effects of progestational agents. This pattern of interaction is exactly what we observed in our patients at high risk for development of diabetes. It is important to note that we found no increase in the risk of developing diabetes associated with breastfeeding, per se, among women who used nonhormonal contraception in the present study or in a previous report of women with prior GDM.²⁷ Thus, it is unlikely that the increased diabetes rate observed during progestin-only OC use was due to breast-feeding alone, although the low-estrogen state associated with breast-feeding may have enhanced any diabetogenic effects of the progestin-only preparation. Whether progestin-only contraceptive agents will be diabetogenic in high-risk women who are not breast-feeding remains to be determined. Likewise, our study does not reveal whether any hyperglycemia that develops during progestin-only OC use

will abate after cessation of use. However, the deleterious effects of "glucose toxicity"^{28,29} on pancreatic β -cell function suggest that such an effect could lead to progressive worsening of hyperglycemia and, therefore, cannot be ignored.

The apparent safety of low-dose progestin and estrogen combination OCs in women with prior GDM is in keeping with our prior experience¹³ and with reports of other investigators^{11,12,30,31} from studies that were much smaller and were conducted for shorter amounts of time than the present investigation. For example, we¹³ previously found that neither of the 2 combination OC preparations used most frequently in the present study altered glucose tolerance over a 6- to 13-month period in a smaller number of women with prior GDM compared with a parallel group of women using nonhormonal contraception. Skouby and colleagues¹¹ reported no change in oral glucose tolerance in women with prior GDM during 6 months of treatment with a triphasic or monophasic combination OC³² containing levonorgestrel. However, insulin levels were increased during combination OC use, particularly with the higher-dose, monophasic preparation (0.150 mg of levonorgestrel). Moreover, glucose clamp studies with women taking the triphasic preparation indicated a significant reduction in insulin sensitivity despite maintenance of normal glucose tolerance for 6 months.¹² This finding, coupled with evidence that insulin resistance may accelerate the development of diabetes in women with prior GDM,⁹ raised concern about the long-term safety of combination OCs in these high-risk patients. However, we found no evidence for an acceleration of the diabetes rate after up to 5 years of continuous use of OCs in relatively large numbers of subjects, suggesting that any insulin resistance induced by combination OCs was insufficient to induce diabetes during that time period.

The diagnosis of diabetes in this study was made by OGTT. This approach is advantageous in allowing the detection of diabetes at its earliest stage, before the development of symptomatic hyperglycemia or long-term diabetic complications. However, glucose tolerance testing was performed more frequently during OC use than during use of nonhormonal forms of contraception. This fact created a potential bias in the ascertainment of diabetes rates by traditional life-table methods, which assign the onset of diabetes to the date of the first diabetic OGTT. Groups that are tested less frequently (eg, nonhormonal contraceptive users) will have an artifactual lowering of their diabetes rate because of a delay in diagnosis. Interval-censored analysis avoided this bias by treating event times as unknowns within a specified interval and comparing diabetes rates only for individuals actually tested during specified intervals. This analysis revealed no increase in the risk of diabetes during long-term use of combination OCs, but a significant increase in the risk of diabetes during the use of the progestin-only OC. However, interval-censored analysis did not allow adjustment for potential confounding variables and could not accommodate time-dependent variables. Therefore, we cannot exclude an independent effect of combination OCs to increase or decrease the risk of diabetes compared with that found among users of nonhormonal contraception. Any such effect must have been very small, given the large number of subjects who used combination OCs and the great similarity of their diabetes rate to the rate observed in users of nonhormonal contraception (3-year cumulative incidence rates of 25.4% and 26.5%, respectively).

Since combination and progestin-only OC users were tested at the same intervals, Cox proportional hazards regression analysis could be used to compare diabetes risks during use of these 2 forms of contraception. This allowed adjustment for potential confounders and used all follow-up data, including data obtained after switching contraceptive methods. This analysis demonstrated a clearly independent effect of the progestin-only OC to increase the risk of developing diabetes, at least when it was prescribed during the period of breastfeeding for up to 2 years.

Our results have important implications for the clinical care of women with a history of GDM. Additional pregnancies after the index pregnancy complicated by GDM increase the risk of type 2 diabetes.^{9,33} Some women may elect to avoid further pregnancies when presented with this information. Other patients require effective family planning in order to

minimize the risk that they will conceive while sufficiently hyperglycemic to impart an increased risk of congenital anomalies to their offspring.³⁴ Thus, contraception is clearly an important issue to all women with a history of GDM.

It is important to note that this study was conducted in a cohort of predominantly obese Latinas and that birth control methods were not randomized among study groups. Thus, we cannot conclude with certainty that the diabetogenic effects of progesterone-only contraception will occur in other ethnic groups or that the effects were not due to some unidentified characteristic of the women who chose to use progesterone-only contraception during breast-feeding. However, since the basic mechanisms underlying type 2 diabetes in Latinas (impaired β -cell function in the pres-

ence of insulin resistance³⁵) appear to be shared by other ethnic groups,^{36,38} we believe it prudent to conclude that progestin-only contraception should be used with caution, if at all, in breast-feeding women with a history of GDM. Nonhormonal methods are associated with a lower risk of developing diabetes during breast-feeding and are preferable in that setting. Our results also provide strong rationale for the conduct of randomized clinical trials to assess more precisely the impact of different forms of contraception in women at high risk of developing diabetes.

In summary, this study in Latinas with recent GDM did not reveal an increase in the risk of developing type 2 diabetes during long-term use of low-dose progestin and estrogen combination OCs compared with use of nonhor-

monal contraception. By contrast, use of a progestin-only OC preparation during breast-feeding was associated with nearly a 3-fold increase in the risk of diabetes. Our results indicate that low-dose combination OCs can be used safely in women with recent GDM. By contrast, use of progestin-only OCs during breast-feeding, if prescribed at all, should be accompanied by careful monitoring of blood glucose concentrations in these high-risk women.

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