Long-Acting Injectable Progestin Contraception and Risk of Type 2 Diabetes in Latino Women With Prior Gestational Diabetes Mellitus

ANNY H. XIANG, PHD[1]
MIWA KAWAKUBO, MS[1]

SIRI L. KJOS, MD[2,3]
THOMAS A. BUCHANAN, MD[2,4]

OBJECTIVE — To investigate the impact of a long-acting injectable progestin, depo-medroxyprogesterone acetate (DMPA), compared with combination oral contraceptives (COCs) on the risk of diabetes in Latino women with prior gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS — An observational cohort study of 526 Hispanic women with prior GDM who were not diabetic in their postpartum visit during January 1987 to October 1997 and who elected DMPA ($n = 96$) or COCs ($n = 430$) as initial contraception were followed for a maximum of 9.2 years with a median follow-up of ~12 months. Oral glucose tolerance tests were performed and choice of contraception method was recorded at each visit as part of routine clinical care.

RESULTS — Annual diabetes incidence rates were 19% in the DMPA group and 12% in the COC group, with an unadjusted hazard ratio (HR) of 1.58 (95% CI 1.00–2.50; $P = 0.05$) for DMPA compared with COCs. Adjustment for baseline imbalances reduced the HR to 1.18 (0.67–2.28; $P = 0.57$). Additional adjustment for weight gain during follow-up, which was on average 1.8 kg higher in the DMPA group ($P < 0.0001$), reduced the HR to 1.07. DMPA interacted with baseline serum triglyceride levels and, separately, with breast-feeding to increase the diabetes risk.

CONCLUSIONS — DMPA use was associated with an increased risk of diabetes that appeared to be explained by three factors: *1*) use in women with increased baseline diabetes risk, *2*) weight gain during use, and *3*) use with high baseline triglycerides and/or during breast-feeding.

Latino women with prior gestational diabetes mellitus (GDM) have a high risk of type 2 diabetes during their reproductive years (1–4), which is increased by additional pregnancies (5). Conceiving with mild, asymptomatic diabetes can double the risk of birth defects in offspring (6), making safe and effective methods of contraception crucial. Among highly effective methods, sterilization (e.g., tubal ligation) and intrauterine devices are metabolically neutral, while metabolic effects of hormonal contraceptives vary according to the specific formulation and dosage (4,7,8). In a prior study, we observed in a group of predominantly Latino women with recent GDM that those who selected low-dose combination oral contraceptives (COCs) had no increased risk of diabetes compared with women who selected nonhormonal contraception (4). By contrast, women who selected progestin-only oral contraceptives while breast-feeding had a nearly threefold excess risk of diabetes that was not explained by breast-feeding per se. Injectable depo-medroxyprogesterone acetate (DMPA) is another progestin-only contraceptive that offers high effectiveness and longer duration. Relatively little has been published regarding the metabolic effect of DMPA in healthy women (9,10) and none regarding its use in women with prior GDM. The present study examines the risk of diabetes associated with DMPA use in subjects derived from the same patient population as our prior study of combination and progestin-only oral contraceptives and nonhormonal contraception (4).

RESEARCH DESIGN AND METHODS — In 1987, we initiated a follow-up program of glucose tolerance testing of women with prior GDM at Los Angeles County Women's and Children's Hospital's High-Risk Family Planning Clinic. The cohorts for several publications have been derived from these patients (1,4,5), of whom ~97% have Spanish surnames and were born in Mexico or Central America. Women with GDM were scheduled for a 75-g oral glucose tolerance test (OGTT) 4–6 weeks postpartum in combination with a standard family planning visit. Women who returned for the postpartum test were scheduled for annual OGTT testing thereafter. Women who elected to use hormonal contraception were scheduled for an additional OGTT 3–6 months after method initiation. Women also returned for interim visits in the event of an intercurrent medical problem, a desire to change methods, and every 6 months for COC refills or every 3 months for DMPA injections. OGTTs were not performed at interim visits, but blood pressure, weight, and systems review were obtained. At each OGTT visit, women underwent a

physical examination, contraceptive counseling, and were advised to exercise daily and attain or maintain ideal body weight. When impaired glucose tolerance or abnormal lipid levels were found, subjects received additional lifestyle counseling and a nutritionist appointment. When diabetes, the study end point, or overt lipid abnormalities (e.g., total cholesterol ≥240, LDL cholesterol ≥160, HDL cholesterol ≤55, or triglycerides ≥500 mg/dl) (11) were found, subjects were referred to a medicine clinic.

Data for analyses are from women who *1*) did not have diabetes at the initial postpartum OGTT, *2*) initiated contraception with either DMPA or COCs at the first documented postpartum visit, and *3*) had at least one additional OGTT before switching to a nonstudy contraceptive or becoming pregnant. The comparator group was limited to women who selected COCs for two reasons. First, COCs did not increase the risk of diabetes compared with nonhormonal methods (4). Second, the frequency of 1st-year diabetes testing was similar in women using DMPA and COCs, eliminating potential bias in diabetes rates due to differences in testing frequency. This study was approved by University of Southern California Institutional Review Board.

Selection of contraception

At the postpartum visit, subjects were given standardized education regarding contraceptive methods and were permitted to select their desired method, irrespective of age or initial metabolic status. COCs were not prescribed for subjects with known hypertension, elevated blood pressure (≥140/90 mmHg), cardiovascular disease, or current cigarette use. During follow-up, subjects were permitted to change methods of contraception. For nonbreast-feeding women who elected COCs (COC group), either a monophasic norethindrone preparation (0.40 mg norethindrone and 35 μg ethinyl estradiol) or a triphasic levonorgestrel preparation (0.05–0.125 mg levonorgestrol and 30–40 μg ethinyl estradiol) was prescribed according to clinic protocol for prior GDM, with individualized deviations approved by the medical director (S.L.K.). Women who elected DMPA (DMPA group) contraception received 150-mg intramuscular injections every 12 weeks.

Testing procedures

OGTTs were conducted on sitting subjects after a 10- to 12-h overnight fast. Subjects were advised to eat three meals and a snack daily for 3 days before testing. Blood, obtained by venipuncture before and at 30, 60, 90, and 120 min after glucose ingestion, was placed into heparin-fluoride–containing tubes. Plasma was separated and assayed for glucose using a Beckman Glucose Analyzer CX4 (Beckman Instruments, Brea, CA). Fasting blood samples for serum lipid determinations were drawn into tubes without anticoagulants, and serum was separated after the blood was allowed to clot for 1 h. Total serum cholesterol and triglyceride concentrations were measured by enzymatic hydrolysis and oxidation. HDL cholesterol levels were determined by oxidation after precipitation of LDL and VLDL cholesterol. LDL cholesterol levels were estimated as (total cholesterol) − (HDL cholesterol) − (total triglycerides/5), unless triglycerides were ≥400 mg/dl, in which case LDL cholesterol was not estimated. Blood pressure was measured with an aneroid sphygmomanometer after patients had been sitting for at least 5 min.

Data analysis

Baseline and follow-up characteristics were compared between the DMPA and COC groups using the two-group *t* test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Log transformation was applied for nonnormally distributed variables before *t* tests. Durations of follow-up and of uninterrupted use of the initial contraceptive method were compared between groups by Wilcoxon's rank-sum test. Total area under the curve for plasma glucose during OGTTs was calculated by the trapezoid method. Diabetes was diagnosed by OGTTs based on American Diabetes Association criteria (12). Data are presented as means ± SD in tables and text. Data were analyzed to address the following two questions.

Was DMPA use associated with any risk of diabetes in women with prior GDM? Person-year and Kaplan-Meier survival methods were used, respectively, to estimate average annual diabetes incidence rates and cumulative diabetes incidence rates by initial contraceptive method. Cox proportional hazard regression analysis was used to estimate the unadjusted and adjusted relative risk of developing diabetes in the DMPA group compared with the COC group. DMPA use (yes/no) was treated as a time-dependent variable to include data for women who switched between groups during the study period. Possible lag or prolonged effect of DMPA was examined by evaluating effects began and/or ended 1–6 months from the actual dates of use. No indication of lag or prolonged effect was found, so results from models with no temporal effects are presented. The proportional hazard assumption was evaluated by testing time and group interaction and no significant violation was observed. The adjusted analyses included as covariates all baseline unbalanced variables and weight change during follow-up. Weight change was included as a time-dependent covariate.

Was there any particular group of women that might be susceptible to an increased diabetes risk during DMPA use? Baseline age, BMI, parity, diabetes in family, fasting glucose, OGTT glucose area, blood pressure, and lipids were evaluated for possible modification of a DMPA effect by testing the interaction between each of these baseline variables and use of DMPA compared with COCs. Because COCs were not prescribed in breast-feeding women, we could not assess interactions between breast-feeding and the two study groups. Accordingly, effect modification associated with breast-feeding was evaluated by comparing the risks of diabetes among three groups: DMPA with breast-feeding, DMPA without breast-feeding, and COC without breast-feeding. Since not all women who breast-fed at baseline continued the breast-feeding throughout the entire observation period, breast-feeding was treated as a yes/no time-dependent variable. All reported *P* values were two sided. A *P* value of 0.05 was accepted as statistically significant.

RESULTS — A total of 526 women met the subject selection criteria, 96 who initially elected DMPA and 430 who initially elected COCs. Of 430 women in the COC group, 67% received monophasic norethindrone (Ovcon) and 25% received the triphasic levonorgestrel (Triphasil). The remaining 8% all received COCs containing low-dose estrogen (<35 μg) with varying doses of norethindrone (≤1.0 mg) or levonorgestrel (≤0.150 mg). At baseline (Table 1), the DMPA and COC groups were similar with regard to the frequency of insulin treatment during the index pregnancy

Table 1—*Baseline characteristics in women who elected DMPA or low-dose COCs as initial method of contraception**

	DMPA	COCs	P value†
n	96	430	
Insulin treated during index pregnancy	12.5	13.1	0.88
Age (years)	30.0 ± 5.5	29.0 ± 5.5	0.13
BMI (kg/m²)	30.4 ± 6.1	28.3 ± 4.4	0.002
Parity	2.6 ± 1.6	2.3 ± 1.3	0.10
Diabetes in family (%)	22.9	10.2	0.0007
Breastfeeding (%)	22.9	0	<0.0001
Fasting glucose (mg/dl)	91.5 ± 9.5	91.6 ± 10.5	0.97
OGTT glucose AUC (mg · dl⁻¹ · min⁻¹ per 10³)‡	15.8 ± 3.1	16.4 ± 3.4	0.11
Impaired glucose tolerance§	21	27	0.20
Systolic blood pressure (mmHg)	114.4 ± 14.3	112.2 ± 10.8	0.16
Diastolic blood pressure (mmHg)	66.7 ± 10.2	67.5 ± 9.6	0.44
Total cholesterol (mg/dl)	204.5 ± 41.7	206.1 ± 38.0	0.72
HDL cholesterol (mg/dl)	38.6 ± 11.2	45.7 ± 12.0	<0.0001
LDL cholesterol (mg/dl)	133.2 ± 32.5	126.0 ± 34.5	0.07
Triglycerides (mg/dl)	157.0 ± 95.9	180.6 ± 102.1	0.01

Data are means ± SD or frequency percent, unless otherwise indicated. *At initial postpartum visit for OGTT and selection of method of contraception. †From t test or χ^2 or Fisher's exact test. For triglycerides, log transformation was applied prior to t test. ‡Total area under glucose curve (AUC), calculated by trapezoid rule. §Impaired glucose tolerance defined by 2-h OGTT glucose ≥140 and ≤199 mg/dl.

(prescribed for persistent fasting glycemia ≥105 mg/dl) and baseline age, parity, OGTT glucose, blood pressure, and total cholesterol. The DMPA group had significantly higher baseline BMI and frequency of diabetes in family members and lower HDL cholesterol and triglyceride levels. At entry, 23% of women in the DMPA group were breast-feeding.

The medians and interquartile ranges for length of follow-up were 11.3 (14.2) and 12.0 (21.3) months in the DMPA and COC groups, respectively ($P = 0.44$). The median months of uninterrupted use of initial contraception method were 11.2 and 12.0 months, respectively ($P = 0.15$). Only 11 women switched between DMPA and COCs during follow-up, 7 who started with DMPA and 4 who started with COCs. For the 22 women who were breast-feeding at baseline, the median duration of breast-feeding was 5.9 months with a range of 2.3–26.7 months. The DMPA group had significantly more weight gain than the COC group (2.1 ± 3.6 vs. 0.3 ± 2.8 kg; $P < 0.0001$).

Was DMPA use associated with any risk of diabetes in women with prior GDM?

During follow-up, 106 women developed diabetes, 23 of 96 in the DMPA group and 83 of 430 in the COC group. The corresponding numbers were 22 of 96 with uninterrupted DMPA use and 82 of 430 with uninterrupted COC use. Person-year annual incidence rates according to initial method were 19.1% in the DMPA group and 11.9% in the COC group. The corresponding numbers were 19.8% with uninterrupted DMPA use and 11.9% with uninterrupted COC use. The Kaplan-Meier plot of cumulative incidence rates of diabetes by uninterrupted use of DMPA or COCs (Fig. 1) suggests that incidence rates were higher in the 1st compared with later years of use for both DMPA (22.6 vs. 7.4% per year) and COCs (15.0 vs. 5.8% per year). The higher 1st year rates could be due in part to the additional OGTT administered 6 months after starting contraception.

Cox regression analysis examining DMPA use as a time-dependent variable provided an unadjusted hazard ratio (HR) of 1.58 (95% CI 1.00–2.50; $P = 0.05$) compared with COC use. Analysis assuming two separate HRs, one for the 1st year of use and one for subsequent years of use, did not provide better model fitting than the single HR model. Thus, one constant HR across follow-up time best described the risk pattern.

Since DMPA users had higher baseline BMIs, rates of breast-feeding, and family members with diabetes and lower HDL cholesterol and triglyceride levels, analysis was repeated with these five baseline variables as covariates. After adjusting for these covariates, the risk associated with DMPA use decreased from 1.58 to 1.18 (95% CI 0.67–2.28; $P = 0.57$). Additional adjustment for weight gain during follow-up further reduced the risk estimate to 1.07 (0.61–1.89; $P = 0.81$).

Was there any particular group of women that might be susceptible to an increase in diabetes risk during DMPA use?

Only baseline triglycerides, but not baseline age, BMI, parity, diabetes in family, fasting glucose, OGTT glucose area, blood pressure, total cholesterol, HDL cholesterol, and LDL cholesterol, interacted significantly with DMPA use to alter the risk of diabetes ($P = 0.04$). When baseline triglyceride levels were dichotomized at the cohort median (150 mg/dl),
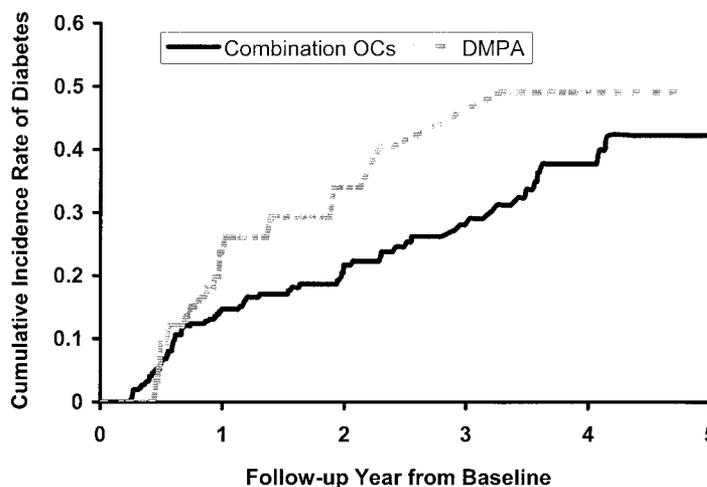
Figure 1—*Kaplan-Meier plot of cumulative incidence rate of type 2 diabetes by uninterrupted use of DMPA or COCs for the first 5 years after postpartum. For the 11 women who switched methods, data were used up to the time when switch occurred.*

Table 2—Unadjusted and adjusted HR of developing diabetes associated with uninterrupted use of each initial method of contraception and with 1) baseline triglycerides below or above the cohort median of 150 mg/dl and 2) with or without breast-feeding*

	Unadjusted		Adjusted†	
	HR (95% CI)	*P* value†	HR (95% CI)	*P* value†
Triglyceride interaction	1.00	—	1.00	—
COCs and below median (*n* = 206, mean TG = 108 mg/dl)‡				
DMPA and below median (*n* = 57, mean TG = 97 mg/dl)	1.02 (0.47–2.22)	0.95	0.55 (0.22–1.31)	0.20
COCs and above median (*n* = 224, mean TG = 248 mg/dl)	1.53 (1.00–2.37)	0.059	1.39 (0.88–2.19)	0.16
DMPA and above median (*n* = 39, mean TG = 245 mg/dl)	3.85 (2.04–7.24)	<0.0001	2.28 (1.08–4.81)	0.03
Breast-feeding interaction				
COCs without breast-feeding (*n* = 430)‡	1.00	—	1.00	—
DMPA without breast-feeding (*n* = 74)	1.28 (0.72–2.27)	0.40	1.06 (0.58–1.95)	0.85
DMPA with breast-feeding (*n* = 22)	3.45 (1.57–7.57)	0.002	2.21 (0.96–5.11)	0.06

*For the 11 women who switched methods, data were used up to the time when switch occurred. †Adjusted for baseline unbalances of BMI, diabetes in family, breast-feeding status (in analyses for triglyceride [TG] interactions), triglycerides (in analyses for breast-feeding interactions), HDL cholesterol and weight change during follow-up. †By Cox regression analysis. ‡Reference group for HR calculation.

there was no significantly increased diabetes risk in DMPA users with triglycerides <150 mg/dl or in COC users with triglycerides >150 mg/dl compared with the reference group, who were COC users with baseline triglycerides <150 mg/dl (Table 2). Only DMPA users with baseline triglycerides above the median had a significantly higher diabetes risk (adjusted HR 3.85, unadjusted HR 2.28) compared with the reference group. Not shown in Table 2 are the diabetes risks for high versus low triglycerides within the DMPA group (adjusted HR 4.49 [95% CI 1.57–12.8], *P* = 0.01) and the risk of DMPA versus COCs in women with triglycerides above the cohort median (1.65 [0.83–3.29], *P* = 0.15). Thus, the risks of diabetes associated with either DMPA or high baseline triglycerides depended upon the presence of the other factor. Either one alone had no increase or a modest increase in risk. The two combined resulted in more than additive effect in increasing risk.

There also was an interaction between breast-feeding and DMPA (Table 2). Compared with COC use, DMPA use without breast-feeding was associated with no increase in the risk of developing diabetes, but DMPA use with breast-feeding significantly increased the risk of diabetes (unadjusted HR 3.45, adjusted HR 2.21). Even within the DMPA group, the 22 women who breast-fed had a more than twofold increase in adjusted diabetes risk compared with the 74 who did not (adjusted HR 2.21 [95% CI 0.69–7.02], *P* = 0.18), although this difference was not statistically significant.

CONCLUSIONS — We found that Latino women with prior GDM who, with

the advice of their care providers, elected to use DMPA had an increased risk of developing diabetes compared with women who elected to use COCs. However, the increased risk appeared to be due to a combination of factors. First, baseline differences in weight, breast-feeding status, family history of diabetes, and lipids appeared to account for much of the difference in diabetes risk between DMPA and COC groups. This finding may reflect prescribing or patient selection bias at the initial selection of contraceptive method. Second, weight gain during DMPA use may have contributed in a small way to increased diabetes risk. Third, use of DMPA with relatively high baseline triglycerides or during breast-feeding increased the risk of diabetes.

Our finding of increased risk associated with DMPA use in combination with breast-feeding is consistent with our previous report from the same high-risk patient group (4). In that report, we found that the progestin-only oral contraceptives (0.35 mg norethindrone), which were prescribed only during breast-feeding, were associated with a 2.9-fold increase in the risk of developing diabetes compared with using of COCs. Breast-feeding per se (i.e., without hormonal contraceptives) was not associated with an increased risk of diabetes; thus, there appears to be an interaction between breast-feeding and use of progestin-only contraceptives that increases blood glucose levels, thereby increasing the incidence of diabetes after GDM. While we have not investigated the physiological mechanism for this interaction, we speculate that exposure to progestins when endogenous estrogen levels are low (e.g., during breast-feeding) may exaggerate

the imbalance between insulin resistance and insulin secretion that is already present in patients with a history of GDM. Our current findings support that speculation, not only in the direction but also in the magnitude of diabetes risk, which was approximately two- to threefold in both of our studies of progestin-only contraception. The risk in the present study was of borderline statistical significance in the adjusted analysis, most likely due to the relatively small number of women who elected DMPA and breastfeed in the present study (22 women) compared with our previous study (78 women) (4); thus, our power is limited.

The interplay among triglyceride levels, contraception, and the risk of diabetes was complex. Neither DMPA use with relatively low triglycerides nor COC use with relatively high triglycerides (i.e., above the cohort median of 150 mg/dl) significantly increased the risk of diabetes compared with COC use with relatively low triglycerides. By contrast, DMPA use with relatively high triglycerides increased the risk more than twofold compared with COC use with low triglycerides. Thus, neither triglycerides nor DMPA use had an important effect to increase diabetes rates alone, but together they increased the risk, demonstrating the significant interaction between the two factors. High triglyceride levels are one marker of insulin resistance (13,14) and, therefore, could identify women in whom any insulin desensitizing effects of progestin-only contraception could be particularly deleterious to glucose regulation. Whether DMPA altered triglycerides or other markers of insulin resistance during follow-up was not assessed. Likewise, sample sizes were too small to test for a

three-way interaction among triglycerides, DMPA use, and breast-feeding. Thus, we can only conclude that use of DMPA in women with relatively high triglyceride levels may increase the risk of diabetes after GDM, at least in one high-risk group.

One other group has published on DMPA use and the risks of diabetes (15) and weight gain (16). Both studies were in Navajo women. A case-control study by Kim et al. (15) showed that DMPA was associated with an odds ratio of 3.6 of developing diabetes compared with COCs in Navajo women aged 18–50 years. No detailed breast-feeding information was reported. A 2-year longitudinal cohort study in the same population by Espey et al. (16) showed that DMPA use was associated with ~2.7 kg/year more weight gain compared with nonprogestin methods. Both the estimated risk of diabetes and the weight gain in the Navajo studies are higher than in our Latino women with prior GDM. Population differences could be a primary contributing factor to the differences. For weight gain associated with DMPA, it has been suggested that progestins may stimulate weight gain and appetite in men as well as in women (17). Note that the DMPA group were more obese at baseline, and obese women may have a tendency of having more weight gain than less obese women. Thus, the increased weight gain in the DMPA group could be a result of both DMPA use and more overweight women.

DMPA has been considered as a good contraceptive choice for women with medical problems, such as hypertension and cardiovascular diseases, that limit the use of estrogen. There is no indication that elevated blood pressure led to the choice of DMPA in this cohort, since baseline blood pressure levels were similar between the DMPA and COC groups and no women had baseline blood pressure >140/90 mmHg. Information on smoking was not collected, although most women in the patient population from which our study cohort was derived do not smoke and none had prior cardiovascular events.

In summary, this prospective observational cohort study in Latino women with prior GDM revealed an increased risk of diabetes in women who elected to use DMPA compared with women who elected to use COCs. Much of the increased risk associated with DMPA was explained by the fact that women selected for DMPA use had clinical characteristics that placed them at increased risk for diabetes even before they started treatment. However, DMPA was associated with increased weight gain that may have slightly contributed to the increased risk for diabetes in women placed on the medication. In addition, use of DMPA during breast-feeding was associated with a more than twofold increase in the risk of diabetes compared with COC and DMPA without breast-feeding. DMPA also appeared to interact with baseline triglyceride levels, increasing the risk of diabetes that was readily detected at triglycerides >150 mg/dl in this study. Our findings in this observational study indicate a need for controlled studies to better define the risks of diabetes associated with the use of DMPA and other hormonal forms of contraception in women at high risk for type 2 diabetes. Pending the results of such studies, our findings suggest a need for caution when considering the use of DMPA in women with prior GDM. Careful monitoring of glucose levels is warranted in women who elect to use the drug, especially in the setting of breast-feeding and/or with high triglycerides.

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