

# A Longitudinal Study of Lipids and Blood Pressure in Relation to Method of Contraception in Latino Women With Prior Gestational Diabetes Mellitus

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**OBJECTIVE** — To investigate the effect of nonhormonal contraception (NHC), combination oral contraception (COC), and depo-medroxyprogesterone acetate (DMPA) on lipids and blood pressure in women with recent gestational diabetes mellitus (GDM).

**RESEARCH DESIGN AND METHODS** — An observational cohort of 972 nondiabetic, normotensive, postpartum Latino women who elected NHC ( $n = 448$ ), COC ( $n = 430$ ), or DMPA ( $n = 94$ ) were followed for at least one subsequent metabolic evaluation on the same contraception. Baseline and follow-up measures included glucose tolerance testing, fasting serum LDL and HDL cholesterol, triglycerides, and systolic (SBP) and diastolic (DBP) blood pressure. Patterns of changes in lipids and blood pressure were evaluated by comparing slopes over follow-up time using random coefficient linear mixed-effects models.

**RESULTS** — Median follow-up times were 20, 12, and 11 months in the NHC, COC, and DMPA groups. The DMPA users gained significantly more weight ( $4.3 \pm 6.9$  kg/year) compared with NHC and COC users ( $1.2 \pm 4.7$  and  $0.7 \pm 6.0$  kg/year, respectively;  $P < 0.0001$ ). Patterns of change in LDL cholesterol, triglycerides, and DBP were not significantly different among groups. HDL cholesterol change differed only between COC and NHC groups (adjusted slopes:  $1.0$  vs.  $-1.6$  mg  $\cdot$  dl<sup>-1</sup>  $\cdot$  year<sup>-1</sup>, respectively;  $P < 0.0001$ ). SBP change differed only between COC and DMPA groups (adjusted slopes:  $1.3$  vs.  $-1.7$  mmHg/year, respectively;  $P = 0.01$ ).

**CONCLUSIONS** — These results, derived predominantly from the initial 1–2 years of treatment in Hispanic women, demonstrate that DMPA was associated with greater weight gain than NHCs or COCs. Other differences in blood pressure and lipid effects were very small. These findings should be taken into account when advising women with recent GDM about their contraceptive choices.

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Women with prior gestational diabetes mellitus (GDM) have a high risk of developing type 2 diabetes during their reproductive years (1–4). Conception in the face of hyperglycemia in the diabetic range can

double the risk of birth defects in offspring (5). Good glucose control before conception can greatly reduce this risk. These three facts make pregnancy planning and, thus, effective contraception, crucial to the health care in women with

prior GDM. Equally important is choosing a contraceptive that is metabolically safe (6,7). Low-dose combination oral contraceptives (COCs) (4,8–13) and depo-medroxyprogesterone acetate (DMPA) do not appear to increase the diabetes risk, with the exception of progestin-only methods in breastfeeding women (4,8) or DMPA in women with hypertriglyceridemia (8). Relatively little has been published regarding the impact of hormonal contraception on other metabolic syndrome components such as abnormal lipids and blood pressure. The present study examines whether COCs, DMPA, and nonhormonal contraceptives (NHCs) have different effects on serum lipids and blood pressure in a clinical cohort of mostly Hispanic women with prior GDM.

## RESEARCH DESIGN AND METHODS

The study cohort has been described previously (1,4,5,14). Briefly, in 1987 we initiated diabetes and lipid screening for women with prior GDM at Los Angeles County Women's and Children's Hospital's High-Risk Family Planning Clinic. Patients were scheduled for a 75-g oral glucose tolerance test (OGTT) and fasting serum lipids 4–6 weeks postpartum and annually thereafter in combination with their contraceptive care. Women who elected hormonal contraception were scheduled for an additional OGTT 3–6 months after initiation. Weight and blood pressure were recorded at each OGTT. Women also returned for interim visits in the event of an intercurrent medical problem, a desire to change contraceptive method, and every 6 months for COC refills or every 3 months for DMPA injections. OGTT and lipid assessments were not performed at interim visits, but blood pressure, weight, and systems review were obtained. During annual visits, women underwent 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 and nu-

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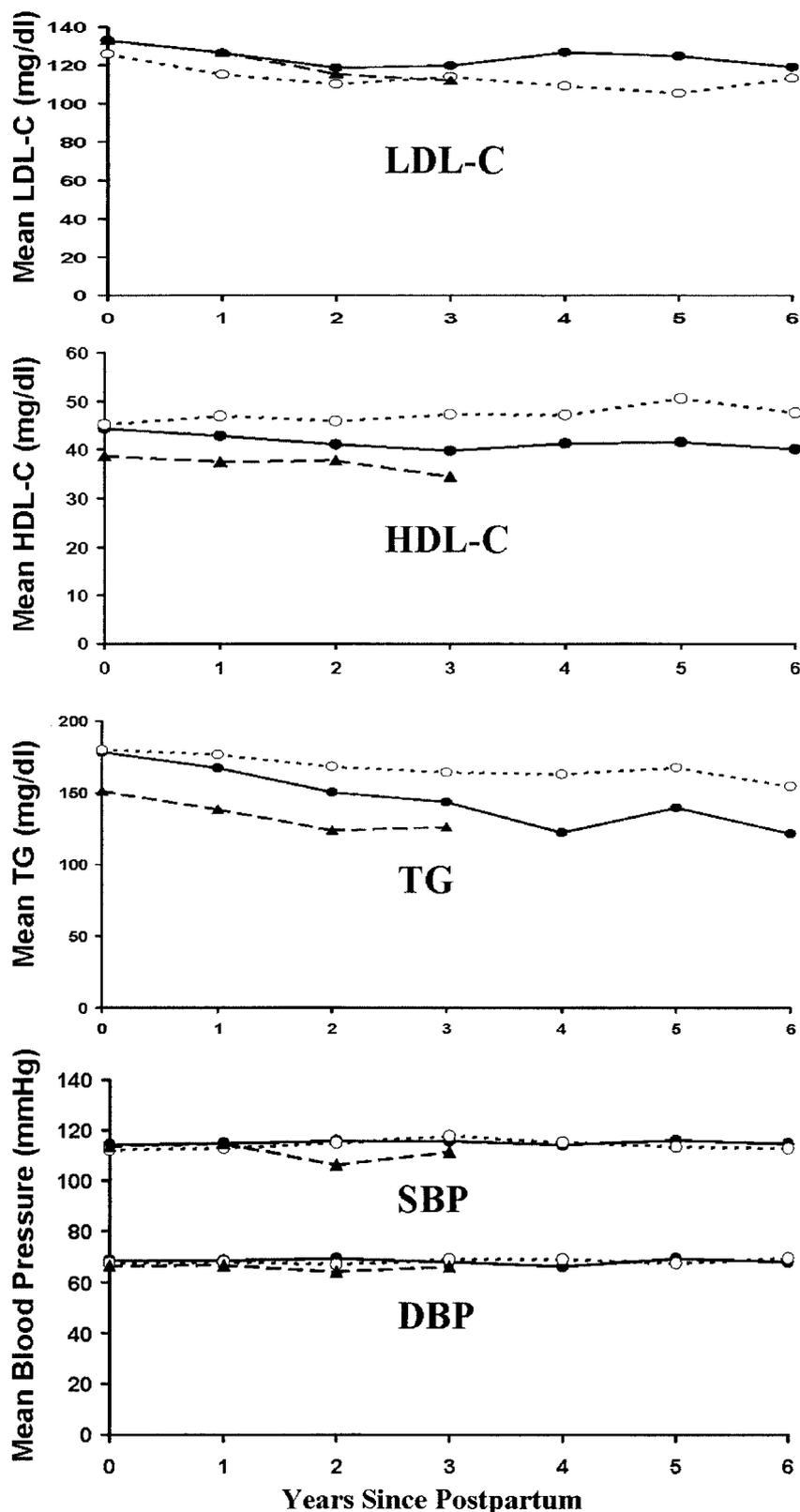
**Abbreviations:** AUC, area under the curve; COC, combination oral contraception; DBP, diastolic blood pressure; DMPA, depo-medroxyprogesterone acetate; GDM, gestational diabetes mellitus; NHC, nonhormonal contraception; OGTT, oral glucose tolerance test; SBP, systolic blood pressure.

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

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**Figure 1**—Mean LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), total triglycerides (TG), SBP, and DBP at annual visits during uninterrupted use of NHCs (●), COCs (○), and DMPA (▲).

low-dose estrogen ( $\leq 35 \mu\text{g}$ ) with varying doses of norethindrone ( $\leq 1.0 \text{ mg}$ ) or levonorgestrel ( $\leq 0.150 \text{ mg}$ ).

At baseline (Table 1), the three groups were similar with regard to the frequency of insulin treatment during the in-

dex pregnancy (prescribed for persistent fasting glycemia  $\geq 105 \text{ mg/dl}$ ), OGTT fasting glucose, and blood pressure. The time since delivery, age, BMI, parity, frequency of diabetes in family members, breastfeeding status, OGTT glucose AUC, and lipids were significantly different among the three groups (Table 1). Differences in time since delivery, age, BMI, parity, and blood pressure were very small. Other differences were more prominent. For example, there was more diabetes in family members and more breastfeeding and lower glucose AUC, triglycerides, and HDL cholesterol in the DMPA group. LDL cholesterol was lower in the COC group.

The median duration of follow-up while continuously using the initial method was significantly longer for the NHC group (20.3 months) compared with the COC and DMPA groups (12.0 and 11.2 months, respectively) (Table 1). The shorter duration of follow-up in the latter two groups was primarily due to exclusion of data after changing methods in the COC group and to later introduction of DMPA into the cohort (available in 1992). The DMPA group gained weight at a significantly higher rate ( $4.3 \pm 6.9 \text{ kg/year}$ ) than either the NHC or the COC groups ( $1.2 \pm 4.7$  and  $0.7 \pm 6.0 \text{ kg/year}$ , respectively;  $P < 0.0001$ ).

Figure 1 depicts the time course of unadjusted mean values for LDL cholesterol, HDL cholesterol, triglycerides, SBP, and DBP by annual visits for the three groups. The mixed-effects model estimates and the comparison of the mean unadjusted and adjusted slopes of change in lipids and blood pressures during follow-up for the three groups are given in Table 2. For LDL cholesterol, the unadjusted slopes were negative for all three groups (range from  $-6.5$  to  $-11.3 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{year}^{-1}$ ), and the slopes were not statistically different among groups ( $P = 0.22$ ). The time between delivery and baseline testing and the baseline values for age, BMI, parity, family history of diabetes, and HDL cholesterol were significantly different among the three groups; they were correlated with follow-up LDL cholesterol in the NHC group ( $P < 0.10$ ). Adjustment for these potential baseline confounders made almost no differences in the comparison of the slopes of LDL cholesterol over time among groups ( $P = 0.25$ ) and neither did adjustment for the potential confounding effect of breastfeeding and weight change during follow-up.

**Table 1—Comparison of baseline characteristics and duration of continuous method use and weight change during the study among the three contraceptive groups**

	NHC	COC	DMPA	P*
n	448	430	94	
Baseline characteristics				
Treated with insulin during index pregnancy (%)	9.6	13.1	11.7	0.28
Median month from index delivery	1.4 (1.3–1.7)	1.4 (1.3–1.6) <sup>a</sup>	1.5 (1.3–1.8) <sup>a</sup>	0.005
Age (years)	31.3 ± 5.7 <sup>a,b</sup>	29.0 ± 5.5 <sup>a</sup>	29.8 ± 5.3 <sup>b</sup>	<0.0001
BMI (kg/m <sup>2</sup> )	29.2 ± 5.0 <sup>a</sup>	28.3 ± 4.4 <sup>a,b</sup>	30.4 ± 6.2 <sup>b</sup>	0.0002
Parity	2.9 ± 1.7 <sup>a</sup>	2.3 ± 1.3 <sup>a</sup>	2.6 ± 1.5	<0.0001
Diabetes in family (%)	8.3 <sup>a</sup>	10.2 <sup>a</sup>	22.3 <sup>a,b</sup>	0.0003
Breastfeeding (%)	7.4 <sup>a,b</sup>	0 <sup>a,c</sup>	23.9 <sup>b,c</sup>	<0.0001
Fasting glucose (mg/dl)	93 ± 10	92 ± 11	92 ± 10	0.12
OGTT glucose AUC (mg/dl × min × 10 <sup>-3</sup> )†	16.7 ± 3.3 <sup>a</sup>	16.4 ± 3.4	15.7 ± 3.0 <sup>a</sup>	0.03
SBP (mmHg)	114 ± 13	112 ± 11	114 ± 13	0.05
DBP (mmHg)	69 ± 11	68 ± 10	66 ± 10	0.09
LDL cholesterol (mg/dl)	133 ± 35 <sup>a</sup>	126 ± 32 <sup>a</sup>	133 ± 33	0.01
HDL cholesterol (mg/dl)	44 ± 11 <sup>a</sup>	45 ± 11 <sup>b</sup>	39 ± 11 <sup>a,b</sup>	<0.0001
Triglycerides (mg/dl)	178 ± 124	180 ± 101 <sup>a</sup>	151 ± 85 <sup>a</sup>	0.01
Characteristics during study period				
Median months of follow-up on continuous contraceptive method	20.3 (12.6–36.5) <sup>a,b</sup>	12.0 (6.2–27.2) <sup>a</sup>	11.2 (6.0–16.2) <sup>b</sup>	<0.0001
Annual weight gain (kg/year)	1.2 ± 4.7 <sup>a</sup>	0.7 ± 6.0 <sup>b</sup>	4.3 ± 6.9 <sup>a,b</sup>	<0.0001

Data are frequency (%), median (lower quartile–upper quartile), or means ± SD. \*From ANOVA or  $\chi^2$  or Fisher's exact test to test for any difference among the three groups. For triglyceride, log transformation was applied prior to analysis. †Total area under glucose curve, calculated by trapezoid rule. a, b, c: groups that share the same letter are significantly different after Bonferroni multiple comparison adjustment, as described in RESEARCH DESIGN AND METHODS.

For HDL cholesterol, the unadjusted slopes were negative in the NHC and DMPA groups but positive in the COC group. The slopes were significantly different among the three groups ( $P < 0.0001$ ); specifically, the slope in the NHC group was significantly lower than the slope in the COC group ( $-1.6 \pm 0.4$  vs.  $1.2 \pm 0.5$  mg · dl<sup>-1</sup> · year<sup>-1</sup>;  $P < 0.0001$ ). Time from delivery to baseline testing and baseline values for age, BMI, family history of diabetes, glucose AUC, LDL cholesterol, triglycerides, and breastfeeding status met the criteria for possible confounders of change in HDL cholesterol. After adjustment, slope in the COC group remained significantly different from the slope in the NHC group and remained so after further adjustment for follow-up breastfeeding and weight change.

For triglycerides, the unadjusted slopes were negative in all three groups (range  $-9.6$  to  $-14.4$  mg · dl<sup>-1</sup> · year<sup>-1</sup>) and were not statistically different among the three groups ( $P = 0.76$ ). Adjustment for baseline potential confounders of time since delivery, age, BMI, parity, glucose AUC, and HDL cholesterol failed to bring out any significant differences in slopes, as did further adjustment for breastfeeding and weight change during follow-up.

The results for blood pressure are given in the bottom of Table 2. In the

absence of adjustments, SBP rose slightly in NHC and COC groups but decreased slightly in the DMPA group. The differences in the slopes among the groups did not approach statistical significance ( $P = 0.17$ ). Adjustment for potential baseline confounders of time since delivery, age, BMI, and glucose AUC had little impact on the results. Further adjustment for differences in breastfeeding and weight change during follow-up lead to a significant difference in SBP slopes among the groups ( $P = 0.04$ ). Specifically, the rate in the COC group was significantly higher than the rate in the DMPA group ( $1.3 \pm 0.4$  vs.  $-1.7 \pm 1.1$  mmHg/year;  $P = 0.01$ ). The difference was primarily due to the adjustment for weight gain in DMPA users ( $1.3$  vs.  $-1.5$  mmHg/year when only weight change was adjusted). For DBP, the slopes were close to zero for all three groups and did not differ significantly among groups whether unadjusted ( $P = 0.88$ ); adjusted for baseline potential confounders of time from delivery to baseline testing, age, BMI, glucose AUC, LDL cholesterol, and triglycerides ( $P = 0.93$ ); or further adjusted for breastfeeding and weight change ( $P = 0.86$ ). All of the above analyses were repeated after excluding the 54 women from the NHC ( $n = 33$ ) and DMPA ( $n = 21$ ) groups who breastfed during the study period. Results

were similar to the adjusted analyses presented above.

**CONCLUSIONS** — While decades of clinical experience and large studies have confirmed the safety and minimal metabolic effects of low-dose COCs (15,16) and DMPA (17) in healthy women, there is a paucity of data examining their use in women at risk for components of the metabolic syndrome, including cardiovascular disease. We previously reported the impact of different forms of contraception on the risk of diabetes in Hispanic women with prior GDM (4,8). The present report adds important information about the impact of contraception on cardiovascular risk factors of obesity, blood pressure, and lipid levels. Our results suggest that COCs can be prescribed without clinically significant effects on weight, serum lipids, or blood pressure in normotensive, nondiabetic Hispanic women with prior GDM. DMPA, on the other hand, is associated with increased weight gain that could, in the long run, prove deleterious to the risk of diabetes (8,14) and possibly heart disease.

In previous short-term, controlled trials examining low-dose COC use in prior GDMs, our group (9) and others (10) did not find significant effects on LDL chole-

**Table 2—Comparison of slopes\* of fasting lipids (LDL and HDL cholesterol and triglycerides) and SBP and DBP over follow-up time among the three contraceptive groups**

Follow-up slope of change	NHC	COC	DMPA	P†
<i>n</i>	448	430	94	
LDL cholesterol (mg · dl <sup>-1</sup> · year <sup>-1</sup> )				
Unadjusted	-6.5 ± 1.2	-9.1 ± 1.4	-11.3 ± 3.4	0.22
Adjusted for baseline‡	-7.2 ± 1.2	-9.4 ± 1.4	-12.1 ± 3.4	0.25
Adjusted for baseline and follow-up‡	-8.3 ± 1.2	-9.7 ± 1.4	-13.3 ± 3.4	0.34
HDL cholesterol (mg · dl <sup>-1</sup> · year <sup>-1</sup> )				
Unadjusted	-1.6 ± 0.4§	1.2 ± 0.5§	-1.5 ± 1.1	<0.0001
Adjusted for baseline‡	-1.7 ± 0.4§	0.9 ± 0.4§	-1.5 ± 1.1	<0.0001
Adjusted for baseline and follow-up‡	-1.6 ± 0.4§	1.0 ± 0.4§	-1.0 ± 1.1	0.0001
Triglycerides (mg · dl <sup>-1</sup> · year <sup>-1</sup> )				
Unadjusted	-14.4 ± 4.1	-9.6 ± 4.9	-12.4 ± 11.3	0.76
Adjusted for baseline‡	-14.2 ± 3.7	-10.1 ± 4.4	-6.3 ± 10.4	0.66
Adjusted for baseline and follow-up‡	-14.7 ± 3.7	-10.4 ± 4.4	-7.6 ± 10.5	0.66
SBP (mmHg/year)				
Unadjusted	1.0 ± 0.3	1.4 ± 0.4	-0.9 ± 1.2	0.17
Adjusted for baseline‡	1.1 ± 0.3	1.5 ± 0.4	-0.9 ± 1.1	0.14
Adjusted for baseline and follow-up‡	0.8 ± 0.3	1.3 ± 0.4§	-1.7 ± 1.1§	0.04
DBP (mmHg/year)				
Unadjusted	0.4 ± 0.3	0.3 ± 0.3	-0.1 ± 0.9	0.88
Adjusted for baseline‡	0.3 ± 0.2	0.3 ± 0.3	0.01 ± 0.9	0.93
Adjusted for baseline and follow-up‡	0.2 ± 0.2	0.2 ± 0.3	-0.3 ± 0.9	0.86

\*Slopes (means ± SE) were estimated from random coefficient mixed-effects model. †From the *F* test with 2 d.f. testing any difference of slopes among all three groups. For triglycerides, log transformation was applied prior to analysis. ‡Baseline-adjusted covariates included time since delivery, time since delivery × follow-up year, age, BMI, and 1) parity, family history of diabetes, and HDL for LDL cholesterol analysis; 2) family history of diabetes, glucose AUC, LDL, triglycerides, and breastfeeding for HDL cholesterol analysis; 3) parity, glucose AUC, glucose AUC × follow-up year, HDL, and HDL × follow-up year for triglyceride analysis; 4) glucose AUC for SBP analysis; and 5) glucose AUC and triglycerides for DBP analysis. Follow-up covariates included weight change and breastfeeding. §Groups that share the same letter are significantly different by Bonferroni multiple comparison adjustment, as described in RESEARCH DESIGN AND METHODS.

terol or triglycerides. In all three groups, the LDL cholesterol and triglyceride levels improved from the baseline postpartum values, possibly due to a physiological return to nonpregnant metabolism (18). The slight increase in HDL cholesterol in COC users was consistent with a previous short-term controlled trial in prior GDM (9) and in normal women (19–23). Although statistically significant, the potential health impact of the very small increase in HDL cholesterol in COC users is unknown.

The association that we observed between COC use and slightly increased SBP is well known. Others have demonstrated increases in both SBP and DBP in healthy women using COCs (24–26). Our COC users had very small positive slopes for both SBP and DBP, but the slopes were on average not significantly different from NHC users. The slope of SBP change was lowest in the DMPA group, so that SBP change in that group was lower than the change in the COC group after adjustment for differences in weight change. This finding suggests that any SBP-lowering benefit of DMPA was counterbalanced at least in part by effect

of weight gain, so that unadjusted SBP was similar across study groups. On average, differences in change in SBP from baseline were very small and not likely to be clinically significant.

Use of DMPA has not been associated with an increase in blood pressure or thromboembolism (26,27). Progestin-only methods do not increase liver globulin production of angiotensinogen and clotting factors. Therefore, DMPA has been considered to be a relatively safe contraceptive option for women with cardiovascular risk factors (28) who desire hormonal contraception. This mindset appeared to be operative in our cohort, in which women who were placed on DMPA were more obese, more likely to have family members with diabetes, and had lower HDL cholesterol levels at baseline than women placed on COCs. We saw no deleterious effects of DMPA on lipids or blood pressure but a significant increase in weight that can contribute to an increased risk of diabetes (8,14).

The significant weight gain in DMPA users has been demonstrated by several other studies. In Navajo women followed for 1 and 2 years, DMPA users gained a

mean of 6 and 11 pounds over the control group (29). In Brazilian women followed for 5 years, DMPA users gained 4.3 compared with 1.8 kg/year for intrauterine device users (30). In obese adolescent girls followed for 18 months, DMPA users compared with COC users and control subjects gained 9.4, 0.2, and 3.1 kg, respectively (31). Obese adolescents appear more susceptible to DMPA-associated weight gain, which manifests as increased total body fat rather than lean mass and may not be due to increased appetite (32). Our study showed a very similar pattern of annual weight gain in DMPA, COC, and NHC users of 4.3, 0.7, and 1.2 kg/year, respectively. The long-term impact of such weight gain on cardiovascular risk is unknown.

Our study has three important limitations. First, assignment to contraception was not done randomly. Subjects and their providers selected contraceptives according to common clinical practice. This fact likely contributed to the differences in baseline characteristics and lengths of uninterrupted use of the initial method. We applied statistical methods that allowed us to adjust for important

confounding variables at baseline and during follow-up. Thus, we were able to sort out in the statistical sense independent effects of contraceptives on selected cardiovascular risk factors. Unadjusted patterns of change may better reflect what will happen in patients clinically. Second, our results should be interpreted with the knowledge that the median duration of continuous use of the same method of contraception was slightly <2 years for NHC and ~1 year for COC and DMPA. Thus, the rates of change that we report occurred mostly over 1–2 years and should not be extrapolated to longer periods of use. Finally, very few women in this cohort smoke, and we did not have quantitative information on frequencies and duration of smoking, so we were unable to examine potential confounding effects due to smoking.

In summary, this prospective observational cohort study in Latino women with prior GDM revealed that patterns of change in serum LDL, triglycerides, and blood pressure after pregnancy were not significantly different among NHC, low-dose COC, and DMPA contraceptive users. Adjusting for baseline differences and follow-up breastfeeding and weight change did not alter these conclusions for LDL cholesterol, triglycerides, and DBP. Adjustment for weight gain identified a small but statistically greater increase in SBP in COC users compared with DMPA users, an effect that was mitigated in part by DMPA-associated weight gain. Patterns of change for HDL cholesterol revealed a very small beneficial effect for COC users that was presented in unadjusted and adjusted analyses. The biggest impact of the contraceptives evaluated was that the weight gain associated with DMPA, which was on average ~4 kg during the 1st year of use. Whether this pattern will persist for longer periods in women with prior GDM is unknown from our data, but studies suggest that it will (29–31). We conclude that COCs and DMPA have very little net impact on lipids and blood pressure in Latino women with prior GDM. However, the weight gain associated with DMPA use suggests that this preparation should be used only with careful attention to nutrition and careful monitoring of body weight and glucose levels in this high-risk group of patients.

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