

Diabetes and Depot Medroxyprogesterone Contraception in Navajo Women

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Background: Depot medroxyprogesterone acetate contraception is widely used in Navajo women, a high-risk population for diabetes mellitus. However, depot medroxyprogesterone may lead to weight gain and independently decrease insulin sensitivity. We studied the association between depot medroxyprogesterone and development of diabetes in Navajo women.

Methods: We studied Navajo women aged 18 to 50 years who had seen a health care provider at a Navajo Area Indian Health Service clinic at least once in 1998. Diabetic cases (n=284) and nondiabetic controls (n=570) were matched by age. Medical records were reviewed to determine contraception use before the diagnosis date of diabetes.

Results: Users of depot medroxyprogesterone were more likely to develop diabetes than patients who had used combination estrogen-progestin oral contraception only (odds

ratio [OR], 3.8; 95% confidence interval [CI], 1.8-7.9). The excess risk persisted after adjustment for body mass index (OR, 3.6; 95% CI, 1.6-7.9). Longer use was associated with greater risk of diabetes. Users of depot medroxyprogesterone were also more likely to develop diabetes than patients who had never used hormonal contraception, although excess risk was smaller (OR, 2.4; 95% CI, 1.4-3.6).

Conclusions: Depot medroxyprogesterone contraception was associated with a greater risk of diabetes compared with combination oral contraceptive use only. Risk was associated with length of use and persisted after adjustment for body mass index. Additional research is needed for confirmation, but this risk should be considered in contraceptive choice for women at high risk for diabetes.

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SINCE ITS introduction in the 1960s, depot medroxyprogesterone acetate has been an effective hormonal contraceptive, but results of studies of possible side effects are inconsistent.¹ Some metabolic studies in populations at low risk for type 2 diabetes mellitus demonstrate decreased glucose tolerance,² increased insulin levels,³ and weight gain¹ in depot medroxyprogesterone users, but others show no change in these variables.^{4,5}

Members of the Navajo tribe are at high risk for type 2 diabetes, with a prevalence of diabetes between 10% and 15% in women aged 20 years and older.^{6,7} A recent longitudinal study in the Navajo indicated that depot medroxyprogesterone is associated with weight gain, a major risk factor for type 2 diabetes mellitus.⁸ However, depot medroxyprogesterone reduces the number of pregnancies, which may also be a risk factor for type 2 diabetes.^{9,10} Therefore, the overall risk of dia-

betes in Navajo users of depot medroxyprogesterone is unclear.

Depot medroxyprogesterone was first introduced on the reservation in 1971 through the Indian Health Service (IHS) hospitals and was used on a limited basis as an alternative contraceptive until formal Food and Drug Administration approval in 1992. Since approval, depot medroxyprogesterone use has increased dramatically. Centralized tracking of prescription by patient is not yet available. However, data from the Navajo Area Supply Service Center, the pharmaceutical distribution center for all Navajo Indian Health hospitals and clinics, show that 491 doses of depot medroxyprogesterone were distributed in 1993 and 16 308 doses were distributed in 1997.⁸

In this study, we determined the risk of diabetes associated with depot medroxyprogesterone use in Navajo women compared with combination estrogen-progestin oral contraception (OC), and whether any risk was independent of

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SUBJECTS AND METHODS

The Navajo Nation consists of more than 200 000 members and is located in the southwestern United States in an area roughly the size of West Virginia.¹³ The IHS, a branch of the Public Health Service, provides free medical care for this population and provides depot medroxyprogesterone contraception along with other types of contraception. The Navajo Nation Institutional Review Board approved the study.

This case-control study included 854 patients who met the following criteria: (1) age of 18 to 50 years, (2) membership in the Navajo Nation, and (3) at least 1 outpatient visit to a health care provider at Gallup Indian Medical Center, Gallup, NM, or Crownpoint Healthcare Facility, Crownpoint, NM, between January 1, 1998, and December 31, 1998. We defined *cases* as eligible patients who had been diagnosed as having type 2 diabetes mellitus by December 31, 1998. We defined *controls* as eligible patients without a diagnosis of type 2 diabetes, age-matched to the cases within 12 months. From a list of all eligible patients, cases were randomly selected, and 2 controls were selected randomly for each case. Four physicians abstracted a total of 284 cases and 570 controls from clinic medical records. We performed a power calculation for the primary comparison of depot medroxyprogesterone with OCs. Assuming that depot medroxyprogesterone exposure with and without OC exposure was 7%, we calculated that 282 cases and 564 controls were required to detect an odds ratio of 2 with a 2-sided $\alpha = .05$ and $\beta = 0.20$. For the comparison of

depot medroxyprogesterone with no hormonal contraception use, we had a power of 0.55 to detect an odds ratio of 2.

The information abstracted included most recent weight and height, blood pressure, hemoglobin A_{1c} level if available, glucose measurement in the past year in control subjects, gestational history, number of visits to the clinic, and hormonal and nonhormonal contraceptive history, including type and date of last use. Contraceptive use was documented up to the date of diabetes diagnosis for each case and her matched control subjects. Patients who had ever used depot medroxyprogesterone were grouped together in 1 category. Patients who had used only combination OC, which included both an estrogen and a progestogen component, were grouped together in 1 category. Patients who never used hormonal contraception and patients who had used levonorgestrel (Norplant; Wyeth-Ayerst Laboratories, Philadelphia, Pa) or progestogen-only pills were categorized separately.

Categorical variables were compared with χ^2 and Fisher exact tests, and continuous variables were compared with *t* tests. Conditional logistic regression models were built by means of Stata software¹⁴ and constructed according to Kleinbaum.¹⁵ Covariates are displayed in several stages; the first stage adjusts for age, the second stage adds most recent body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) measurement, the third stage adds parity, and the fourth stage adds history of gestational diabetes mellitus diagnosed after contraceptives were given. Data are presented as mean \pm SE unless otherwise indicated.

weight gain. We chose to focus on the comparison of risk between depot medroxyprogesterone users and combination OC users, rather than persons who did not use contraception. We did this because, for most women, the primary choice is between varying formulations of hormonal contraception. Hormonal contraception is the most effective method of contraception, with the exception of the intrauterine device and surgical sterilization, which are not recommended for nulliparous women.¹¹ In addition, persons who use contraception tend to be a healthier population than those who do not use contraception.¹²

RESULTS

Demographics of diabetic cases and their controls are described in **Table 1**. Cases had a higher mean arterial blood pressure and BMI, and more often had a history of gestational diabetes. They also had a higher average number of visits in 1998 than nondiabetic subjects. Number of pregnancies and births did not differ significantly between cases and controls. About 84% ($n = 477$) of nondiabetic subjects had a glucose check in 1998, the majority of which were random glucose determinations with a mean level of 100 ± 18 mg/dL (5.6 ± 1.0 mmol/L). None of the random glucose measurements exceeded 200 mg/dL (11.1 mmol/L). The duration of diabetes was 6.0 ± 4.6 years.

Table 2 compares these variables for patients who used depot medroxyprogesterone with or without combination contraception vs patients who used combination contraception only and patients who never used

Table 1. Selected Measures in Patients With Diabetes and Control Subjects*

	Diabetes (n = 284)	No Diabetes (n = 570)	P†
Average mean arterial pressure, mm Hg	92.7 (0.7)	89.1 (0.5)	<.001
Body mass index, kg/m ²	33.0 (0.4)	30.6 (0.3)	<.001
Gravidity, No.	3.5 (0.2)	3.7 (0.1)	.27
Parity, No.	3.2 (0.2)	3.2 (0.1)	.83
History of gestational diabetes mellitus, %	38.3	6.0	<.001
History of bilateral tubal ligation, %	24.6	19.8	.11
History of hysterectomy, %	4.9	5.3	.73
No. of visits in 1998	8.5 (0.5)	5.8 (0.2)	<.001

*Data are given as mean (SE) unless otherwise indicated.

†P value obtained from conditional logistic regression.

hormonal contraception. Cases were compared with cases, and controls with controls, to preserve matching characteristics. Among controls, depot medroxyprogesterone users gave birth to significantly more children than combination contraception users and those who never used hormonal contraception. Depot medroxyprogesterone users tended to be younger than patients who never used hormonal contraception and to more frequently have had a history of gestational diabetes mellitus. Among cases, no significant differences existed between depot medroxyprogesterone users and combination users, although depot medroxyprogesterone users tended to be

Table 2. Selected Measures in Depot Medroxyprogesterone Users, Combination Oral Contraceptive Users, and Subjects Who Never Used Hormonal Contraception*

	Depot Medroxyprogesterone Acetate†	OC‡	P	No Hormonal Contraceptive§	P
Control Subjects					
Age, y	36.1 (1.7)	39.1 (0.7)	.07	41.2 (0.4)	.004
Average mean arterial pressure, mm Hg	87.4 (2.1)	89.1 (1.2)	.54	89.2 (0.6)	.49
Body mass index, kg/m ²	30.0 (1.5)	30.5 (0.6)	.77	30.7 (0.3)	.63
Gravidity, No.	4.8 (0.6)	3.8 (0.2)	.08	3.5 (0.1)	.02
Parity, No.	4.6 (0.6)	3.3 (0.2)	.02	3.1 (0.1)	.002
History of gestational diabetes mellitus, No. (%)	4 (19.0)	6 (6.7)	.09	20 (4.7)	.02
Contraceptive given before gestational diabetes diagnosis, No. (%)	1 (4.8)	3 (3.3)	.57	0 (0)	.05
History of bilateral tubal ligation, No. (%)	4 (19)	21 (23.3)	.78	82 (19.2)	>.99
History of hysterectomy, No. (%)	1 (4.8)	4 (4.4)	>.99	25 (5.8)	>.99
No. of visits	7.6 (1.3)	6.1 (0.6)	.28	5.7 (0.3)	.14
Patients With Diabetes					
Age, y	36.8 (1.3)	39.8 (1.2)	.11	40.8 (0.5)	.02
Average mean arterial pressure, mm Hg	93.0 (2.2)	94.6 (1.9)	.59	92.5 (0.8)	.82
Body mass index, kg/m ²	33.6 (1.3)	33.6 (1.5)	.98	32.9 (0.5)	.59
Gravidity, No.	4.2 (0.4)	3.8 (0.4)	.50	3.3 (0.2)	.16
Parity, No.	3.8 (0.4)	3.5 (0.4)	.61	3.0 (0.2)	.14
History of gestational diabetes mellitus, No. (%)	13 (50.0)	16 (55.1)	.70	76 (34.5)	.12
Contraceptive given before gestational diabetes diagnosis, No. (%)	5 (19.2)	9 (31.0)	.37	0 (0)	<.001
History of bilateral tubal ligation, No. (%)	2 (7.7)	8 (27.6)	.08	58 (26.4)	.05
History of hysterectomy, No. (%)	0 (0)	1 (3.4)	>.99	13 (5.9)	.37
No. of visits	8.2 (1.5)	8.0 (1.2)	.90	8.6 (0.5)	.82

*In control subjects, Fisher exact 2-tailed test was used for categorical tests. In patients with diabetes, χ^2 tests were used for categorical tests except for the items "Contraceptive given before gestational diabetes diagnosis," "History of bilateral tubal ligation," and "History of hysterectomy," in which a Fisher exact 2-tailed test was used. Data are given as mean (SE) unless otherwise indicated.

†Ever use (n = 21 for control subjects, n = 26 for patients with diabetes).

‡Combination oral contraceptive (OC) only (n = 90 for control subjects, n = 29 for patients with diabetes).

§n = 428 for control subjects, n = 220 for patients with diabetes.

Table 3. Odds Ratio of Diabetes and Depot Medroxyprogesterone Acetate Use, With Respect to Combination Oral Contraceptive Use Only*

Adjusted for	Any Depot Medroxyprogesterone Use	Duration of Depot Medroxyprogesterone Use			Test for Trend, P
		≤3 mo	4-11 mo	≥12 mo	
Age only	3.8 (1.8-7.9)	1.7 (0.52-5.4)	4.1 (1.4-11)	8.4 (2.5-28)	<.001
Age and body mass index	3.6 (1.6-7.9)	1.9 (0.54-6.6)	4.2 (1.4-13)	5.4 (1.5-20)	.001
Age, body mass index, and parity	3.5 (1.6-7.7)	1.8 (0.52-6.4)	4.2 (1.4-13)	5.2 (1.4-19)	.001
Age, body mass index, parity, and gestational diabetes diagnosed after contraceptive given	4.1 (1.8-9.7)	1.4 (0.30-7.0)	4.8 (1.2-20)	20 (4.0-99)	<.001

*Values are given as odds ratio (95% confidence interval).

younger than those who never used hormonal contraception and to have had bilateral tubal ligations less frequently. Only 5 women used levonorgestrel for an average of 33 ± 27 months, and 40 women had used a progestogen-only pill an average of 4.9 ± 4.8 months.

The risk of diabetes with any history of depot medroxyprogesterone use and with varying lengths of depot medroxyprogesterone use compared with combination OC use only is shown in **Table 3**. History of any depot medroxyprogesterone use was associated with roughly a 4-fold increased risk of diabetes when compared with history of combination OC use only; this risk decreased slightly after adjustment for BMI and after ad-

justment for parity, but still persisted. After adjustment for history of gestational diabetes mellitus diagnosed after contraceptive use, risk increased slightly.

While ever-exposure to depot medroxyprogesterone was not associated with greater BMI when compared with combination OC use, depot medroxyprogesterone exposure of 12 months or more was associated with a BMI greater by 3.6 (odds ratio, 3.6; 95% confidence interval, 0.22-7.1) when compared with combination OC use only. Duration of depot medroxyprogesterone use in months was associated with greater BMI when compared with no hormonal contraceptive use; for every month of use of depot medroxyprogesterone, BMI

Table 4. Odds Ratio of Diabetes and Depot Medroxyprogesterone Acetate Use, With Respect to No History of Hormonal Contraceptive Use*

Adjusted for	Any Depot Medroxyprogesterone Use	Duration of Depot Medroxyprogesterone Use			Test for Trend, P
		≤3 mo	4-11 mo	≥12 mo	
Age only	2.4 (1.3-4.6)	1.1 (0.36-3.3)	2.7 (0.97-7.4)	5.5 (1.7-18)	.004
Age and body mass index	2.1 (1.03-4.2)	1.1 (0.34-3.6)	2.5 (0.87-7.2)	3.2 (0.94-11)	.02
Age, body mass index, and parity	2.1 (1.03-4.3)	1.1 (0.34-3.7)	2.6 (0.88-7.4)	3.2 (0.93-11)	.02
Age, body mass index, parity, and gestational diabetes diagnosed after contraceptive given	1.6 (0.77-3.5)	0.59 (0.16-2.2)	2.1 (0.66-6.8)	3.0 (0.85-11)	.05

*Values are given as odds ratio (95% confidence interval).

was greater by approximately 0.1 (odds ratio, 0.12; 95% confidence interval, 0.001-0.24).

Greater risk of diabetes was associated with longer depot medroxyprogesterone use (Table 3). While use for 3 months or less was not significantly associated with greater risk of diabetes, risk was greater with longer periods of use. Women who used depot medroxyprogesterone for 1 year or more had an almost 8-fold increased risk of diabetes compared with combination OC users. When depot medroxyprogesterone use of 3 months vs 4 to 11 months vs 12 or more months was compared, greater risk of diabetes was associated with longer use. When compared with no history of hormonal contraceptive use, depot medroxyprogesterone was still associated with a doubled risk of diabetes mellitus (Table 4). Again, greater risk of diabetes was associated with longer depot medroxyprogesterone use. The odds ratios were lower than when combination OCs were used as the reference group.

Progestogen-only contraception in the form of a pill or levonorgestrel was not significantly associated with increased risk of diabetes when compared with combination OC use, although the study was underpowered with regard to this type of contraception (odds ratio, 0.87; 95% confidence interval, 0.37-2.1). When combination OC was compared with no history of any type of hormonal contraception, there was a trend toward decreased risk of diabetes mellitus, which reached significance after adjustment for BMI (Table 5).

COMMENT

We found that, when depot medroxyprogesterone was compared with combination OC, depot medroxyprogesterone was associated with greater risk of type 2 diabetes mellitus in Navajo women, and greater risk was associated with longer use. The association between depot medroxyprogesterone and diabetes was partially explained by BMI, but persisted after adjustment for BMI.

Our results must be interpreted with caution, as there are several limitations in design. Because we conducted a clinic-based sampling of cases and controls, the study patients may not be representative of Navajo women. Although the IHS provides free health care to Navajo patients, it is possible that Navajo, even those living on the reservation, receive health care at other facilities. These patients might have received contraceptives that were not recorded in their IHS medical record. If this undetected

Table 5. Odds Ratio of Diabetes and Combination Oral Contraception Use, With Respect to No History of Hormonal Contraceptive Use*

	Odds Ratio (95% Confidence Interval)
Age only	0.65 (0.41-1.1)
Age and body mass index	0.59 (0.36-0.95)
Age, body mass index, and parity	0.62 (0.38-1.01)
Age, body mass index, parity, and gestational diabetes diagnosed after contraceptive given	0.39 (0.22-0.69)

use occurred equally for cases and controls, it would probably bias our results toward the null hypothesis, but it may have magnified the association between diabetes and depot medroxyprogesterone and resulted in selection bias if nondiabetic patients who received contraceptives elsewhere were a healthier population and outside practitioners were more likely to prescribe depot medroxyprogesterone than were IHS practitioners. As a high percentage of diabetic patients may go undiagnosed,¹⁶ misclassification bias may have occurred if the nondiabetic control group actually contained diabetic patients. Although the sensitivity of a random plasma glucose determination has been found to be only about 50% in other populations,¹⁷ more than 80% of our control patients had a glucose level in 1998 that was consistent with absence of diabetes. In addition, this form of bias would also be expected to reduce the association between diabetes and depot medroxyprogesterone use. The association might be magnified if depot medroxyprogesterone users were screened more often for diabetes, resulting in surveillance bias. Depot medroxyprogesterone users had more visits than did combination OC users in the past year, although number of visits in the past year is not a good proxy for screening frequency. Depot medroxyprogesterone users did have urine testing for human chorionic gonadotropin, but this test does not include a urine glucose measurement.

Our conclusions about the relationship between depot medroxyprogesterone, diabetes, and BMI are limited by the cross-sectional nature of the BMI measurement. The most recent measurement was used, and this may not accurately reflect the weight gain that occurred after initiation of contraceptive use. Therefore, although depot

medroxyprogesterone use has been associated with weight gain in a longitudinal study of Navajo women,⁸ our statistical adjustment for BMI is limited.

Patients with gestational diabetes mellitus are at high risk for developing type 2 diabetes, and patients who used depot medroxyprogesterone were significantly more likely to have a history of gestational diabetes.¹⁸ Although the majority were not treated with depot medroxyprogesterone before diagnosis, our study cannot exclude the possibility that certain patient characteristics promote the use of depot medroxyprogesterone as opposed to combination OC use, and that these patient characteristics may be associated with diabetes mellitus. For example, it is interesting that a reason for depot medroxyprogesterone use in patients is theoretically poor patient compliance.¹⁹ In our study, depot medroxyprogesterone users had more children than did combination contraceptive users, although our results cannot distinguish the chronologic order of depot medroxyprogesterone and the pregnancies. It is possible that satisfaction with depot medroxyprogesterone was low, and patients stopped using contraception and subsequently became pregnant, or that patients who had more children subsequently chose depot medroxyprogesterone as a method with easier compliance. However, in their longitudinal study in Navajo women, Espey and colleagues⁸ found that depot medroxyprogesterone-associated weight gain persisted after adjustment for parity.

Patient and provider attitudes toward depot medroxyprogesterone prescription have not been studied in this population. It is possible that providers perceived certain patients to be at higher risk for pregnancy, and these characteristics were also associated with a higher risk for diabetes. For example, patients unable to use other methods of birth control effectively may have been selected for depot medroxyprogesterone, but the barrier to using other birth control could be associated with diabetes. In another scenario, patients who received depot medroxyprogesterone may have engaged in higher-risk sexual behaviors, which could be correlated with poor diet and exercise habits, which in turn put them at higher risk for diabetes mellitus.

The results indicate that depot medroxyprogesterone use may have significant consequences in Navajo women. While previous studies show variable effects of depot medroxyprogesterone on glucose tolerance, the populations studied were at low risk for this complication. The Navajo have a diabetes risk that is much greater than that of the general population across all age groups. Although the majority of diabetic patients are older than 50 years, Navajo women of childbearing age have a 10% risk of having type 2 diabetes.⁶ This rate is double that for the US population as a whole.¹⁶ Therefore, a drug affecting diabetes prevalence has a greater effect in this population.

A mechanism explaining an association between diabetes and depot medroxyprogesterone has not been elucidated. Recent evidence in the Navajo population suggests that long-term depot medroxyprogesterone use is associated with significant weight gain in this population. For patients who used depot medroxyprogesterone for at least 1 year, weight gain was roughly 3 kg greater

than in the OC group, and for patients who used depot medroxyprogesterone for 2 years, weight gain was 6 kg greater.⁸ Since the risk of diabetes increases with BMI,⁶ depot medroxyprogesterone, via weight gain and other pathways, may lead to increased risk of diabetes. Studies of progesterone-only OCs have suggested that the progesterone component may increase insulin resistance in a dose-dependent fashion apart from weight gain,²⁰⁻²² particularly in populations at high risk for diabetes.¹⁸ However, these results are difficult to extrapolate to depot medroxyprogesterone because of the pharmacokinetics of depot release and varying assays used to measure it.²³ In our study, we found no relationship between progesterone-only pill contraception and levonorgestrel contraception and diabetes risk, although length of use of progesterone-only contraception was relatively short and the number of users of levonorgestrel relatively small. Similarly, the continuity of the depot medroxyprogesterone dosing regimen was not significant, but almost all users of multiple doses took their regimen continuously; it is possible that 4 doses given sequentially have different diabetogenic potential than 4 interrupted doses.

Risk of diabetes associated with depot medroxyprogesterone use was greater when compared with risk associated with combination OC use than when compared with risk associated with no hormonal contraception use. This suggests that combination OCs may have a protective effect from diabetes, in addition to depot medroxyprogesterone having a deleterious effect. Previous studies of populations at low risk for diabetes have not found a protective effect of OCs.²⁴ Studies of populations at higher risk for diabetes, such as Latina women with gestational diabetes mellitus, have found that combination OCs seem to offer a protective effect compared with other types of progestin-only contraception and do not increase risk of diabetes compared with nonhormonal contraception.¹⁸ Alternatively, the patients taking combination OCs may be a healthier group at lower risk for developing diabetes.

In Navajo women, a population at high risk for type 2 diabetes mellitus, depot medroxyprogesterone use is associated with greater risk of diabetes. However, depot medroxyprogesterone is an effective means of contraception, and parity may increase risk of diabetes. Therefore, these results must be interpreted carefully. A longitudinal study design that examines diabetes incidence and its relationship to hormonal contraception and weight changes would be useful to confirm the results. Centralized records tracking depot medroxyprogesterone use would assist in understanding prescription patterns and ascertaining sources of confounding. In the meantime, patients should be counseled on the possible increased risk of diabetes-associated depot medroxyprogesterone and the availability of other types of contraception.

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