

# Weight Gain in Obese and Nonobese Adolescent Girls Initiating Depot Medroxyprogesterone, Oral Contraceptive Pills, or No Hormonal Contraceptive Method

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**Objective:** To examine weight changes in a large cohort of obese and nonobese adolescent girls initiating depot medroxyprogesterone acetate (DMPA), an oral contraceptive (OC), or no hormonal contraceptive method (control).

**Design, Setting, and Participants:** Prospective study of 450 adolescent girls, aged 12 to 18 years, who attended 4 urban health clinics and selected DMPA, OC, or control. Data collection occurred at baseline and at 6, 12, and 18 months; consisted of structured interview and measurement of height and weight; and occurred from April 19, 2000, through September 26, 2003.

**Main Outcome Measure:** Weight was examined as mean change over 18 months and actual weight at each study visit. On the basis of preliminary analyses, we stratified the sample according to baseline obesity status (non-obese, body mass index [calculated as weight in kilo-

grams divided by the square of height in meters] <30; obese, body mass index  $\geq 30$  ).

**Results:** Adolescent girls who were obese at initiation of DMPA gained significantly more weight than did obese girls starting OC or control ( $P < .001$  for both). At 18 months, mean weight gain was 9.4, 0.2, and 3.1 kg for obese girls receiving DMPA, receiving OC, and control, respectively. Weight gain in obese girls receiving DMPA was also greater than weight gain in all nonobese categories (4.0 kg, DMPA; 2.8 kg, OC; 3.5 kg, control;  $P < .001$ ). A significant interaction ( $P = .006$ ) between length of time receiving DMPA and weight gain was evident for obese subjects.

**Conclusions:** Over 18 months, DMPA use was associated with increasing rates of weight gain in obese subjects. The potential contribution to severe obesity in this population is concerning.

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**A**MONG ADOLESCENTS RECEIVING depot medroxyprogesterone acetate (DMPA), 41% (27/66) cite weight gain as the primary reason for discontinuing the method.<sup>1</sup> This clinical adverse effect contributes to low DMPA continuation rates among adolescents.<sup>2</sup> At 12 months of use, DMPA continuation rates as low as 27% (43/159) have been reported in this age group.<sup>3</sup>

Despite anecdotal reports of weight gain and documented effects of weight gain on DMPA continuation rates, weight gain has been variable in clinical studies of adolescent girls receiving DMPA.<sup>4,6</sup> Overweight at the time of initiation<sup>7</sup> and race<sup>3,8</sup> have been implicated as risk factors for weight gain, but current studies have been limited by either retrospective data or lack of appropriate control groups.<sup>1,3-9</sup> In addition, little is known about the effect of obesity status on contraceptive adverse effects, since in most controlled studies, either women of

greater body weight were excluded or participants' body weight is not reported.<sup>10</sup>

It is important to understand better the clinical and behavioral context within which weight gain occurs with DMPA so that appropriate anticipatory guidance can be tailored to the individual user. Among adolescent girls, this could result in increased method satisfaction and prolonged use of this effective contraceptive.

The primary objective of this analysis was to examine weight changes prospectively in a large cohort of obese and non-obese adolescent girls initiating DMPA, an oral contraceptive (OC), or no hormonal contraceptive method (control).

## METHODS

### SUBJECTS

The study population consisted of postmenarcheal female subjects aged 12 to 18 years who attended 1 of 4 urban adolescent health clin-

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ics in a large metropolitan setting. Of the 450 subjects who enrolled in the study, 280 (62.2%) identified themselves as black, and 170 (37.8%) identified themselves as not black. Mean chronological age for the sample was 15.5 years, mean menarcheal age was 12.0 years, and mean gynecologic age (chronological age minus menarcheal age) was 3.5 years.

Adolescent girls requesting contraception, and selecting either DMPA or OC, were eligible to participate. In addition, adolescent girls attending the same health clinics, but who planned to receive no hormonal contraception, were eligible for enrollment as control subjects. The control group included adolescents who were abstinent and those using barrier contraceptive methods, although most were not sexually active. Among all 3 groups (DMPA, OC, and control), most study subjects had not received hormonal contraception before the study; 84.9% of subjects initiating DMPA, 97.4% of subjects initiating OC, and 99.3% of control subjects had not received hormonal contraception previously.

Exclusion criteria for subject participation included the following: (1) pregnancy or DMPA use within the preceding 6 months, (2) OC use within the preceding 3 months, (3) alcohol or drug dependence, (4) medical condition or medication use known to be associated with the outcomes of interest (eg, diabetes mellitus, thyroid disease, methylphenidate hydrochloride, divalproex sodium), (5) contraindications to estrogen use, and (6) need for confidential contraceptive care. After a contraceptive method was selected, eligible subjects were told about the study by their health care provider. Those who expressed interest met with a study recruiter to review the protocol. Subjects younger than 18 years gave written assent for participation, and written informed consent was obtained from a parent or legal guardian. Subjects aged 18 years provided their own written informed consent for participation. The study protocol was reviewed and approved by the institutional review board of the participating institutions.

Of the 450 girls recruited at baseline, 115 (25.6%) selected DMPA, 175 (38.9%) selected OC, and 160 (35.6%) were controls. At 18 months, study withdrawal rates according to contraceptive method were as follows: DMPA, 37.4% (43/115); OC, 46.3% (81/175); and control, 25.0% (40/160). Contraceptive continuation rates were markedly higher among study participants than that generally seen in the adolescent population, reported to be from 27% (43/159) to 34% (38/111) at 12 months.<sup>2,3</sup> For subjects receiving DMPA, the 3 most common reasons for study withdrawal were appointment noncompliance (46.5%), withdrawn consent (16.3%), and change of contraceptive method (9.3%). For subjects receiving OC, the major reasons for study withdrawal were appointment noncompliance (24.7%), medication noncompliance (22.2%), and positive pregnancy test (22.2%). For control subjects, the primary reasons for study withdrawal were appointment noncompliance (25.0%), change of contraceptive method (22.5%), and use of nonpermitted contraception (15.0%).

## DATA COLLECTION

The present study represents the 18-month analyses of weight data collected from April 19, 2000, through September 26, 2003, as part of a 2-year study evaluating hormonal contraception and bone mineral density.<sup>11</sup> A major aim of the 2-year study was to evaluate whether estrogen supplementation in subjects receiving DMPA resulted in decreased losses in bone mineral density. As such, DMPA subjects were randomly assigned to receive either monthly injections of estradiol cypionate or placebo. For the present study, subjects receiving DMPA and estradiol and subjects receiving

DMPA and placebo were analyzed separately. No differences in weight gain were seen between the 2 DMPA groups, so data in DMPA subjects were combined.

Baseline data were collected on the day of enrollment and within 1 week after initiating a contraceptive method. Six-month, 12-month and 18-month data were collected on visit days scheduled for contraceptive follow-up, which coincided with time of DMPA injection for subjects using this method. At enrollment, a structured one-on-one interview was conducted to elicit information regarding current age (chronological age); age at menarche (menarcheal age); menstrual regularity; prior contraceptive use; pregnancy history; physical activity; physical and mental health problems; and use of prescription, over-the-counter, and herbal medications. Brief update interviews were conducted at 6, 12, and 18 months. At all visits, weight was measured with a calibrated digital scale, and height was measured with a calibrated stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. To reflect study participants' degree of pubertal maturation, gynecologic age was calculated by subtracting age at menarche from current chronological age.

All subjects received routine contraceptive care from their health care providers as part of their health care visits at baseline and follow-up. Routine care included counseling about potential weight gain, review of healthy eating and exercise habits, monitoring of weight changes, and referral to a registered dietitian if weight concerns arose.

## DATA ANALYSIS

The study purpose was to compare weight gain in adolescents using different contraceptive methods, with the main focus being mean group weight over time; therefore, all data points available at each study visit were eligible for analyses. Preliminary weight analyses demonstrated significant differences between subjects who were nonobese and those who were obese at baseline. The sample was thus stratified according to baseline obesity status (nonobese, BMI <25; overweight, BMI  $\geq$ 25 and <30; obese, BMI  $\geq$ 30). Further analyses demonstrated no differences in weight changes between nonobese and overweight subjects. Therefore, final analyses were performed with the stratification of nonobese and obese (nonobese, BMI <30 and obese, BMI  $\geq$ 30).

Descriptive statistics were means and standard deviations for normally distributed variables, medians and interquartile ranges for nonnormally distributed variables, and counts and percentages for categorical variables. Univariate group comparisons were completed by using  $\chi^2$  tests, analyses of variance, or Kruskal-Wallis tests, as appropriate.

The main outcome measures were defined as change in weight over time and actual weight over time. We used analysis of variance modeling, stratified according to obesity status and adjusted for gynecologic age and race, to explore differences in weight changes among the 3 groups. In addition, unbalanced repeated-measures analysis of variance techniques, stratified according to obesity status and adjusted for gynecologic age and race, were used to examine the relationship between contraceptive method and weight over the 18-month study. Unbalanced repeated-measures analysis of variance techniques were used to adjust for differential withdrawal rates across treatment groups and missing data.

$P \leq .05$  was considered statistically significant. Tukey-Kramer adjustments for multiple comparisons were used as follow-up techniques in the modeling phases of the analyses. Data analyses were conducted with SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC).

**Table 1. Baseline Characteristics of Subjects According to Contraceptive Method\***

Characteristic	All Subjects (N = 450)	DMPA (n = 115)	Oral Contraceptive (n = 175)	Control (n = 160)	P Value†
Obese	94 (20.9)	15 (13.0)	51 (29.1)	28 (17.5)	.002
Chronological age, y	15.5 ± 1.6	15.8 ± 1.5	16.0 ± 1.4	14.9 ± 1.6	<.001
Menarcheal age, y	12.1 ± 1.3	12.0 ± 1.5	12.1 ± 1.3	12.2 ± 1.2	.21
Gynecologic age, y	3.5 ± 1.3	3.9 ± 1.5	3.9 ± 1.3	2.8 ± 1.3	<.001
Weight, kg	65.5 ± 16.8	62.8 ± 14.9	69.3 ± 17.4	63.3 ± 16.8	<.001
BMI, kg/m <sup>2</sup>	25.0 ± 5.9	23.8 ± 4.7	26.4 ± 6.4	24.4 ± 5.8	<.001
Race					.98
Nonblack	170 (37.8)	43 (37.4)	67 (38.3)	60 (37.5)	
Black	280 (62.2)	72 (62.6)	108 (61.7)	100 (62.5)	
Regular menses	377 (83.8)	97 (84.3)	139 (79.4)	141 (88.1)	.16
Previous pregnancy	11 (2.4)	6 (5.2)	5 (2.9)	0 (0.0)	<.001
Physical activity‡					.21
Inactive	40 (9.0)	13 (11.4)	12 (7.1)	15 (9.4)	
Normal	208 (47.2)	58 (50.9)	85 (50.6)	65 (40.9)	
Active	193 (43.8)	43 (37.7)	71 (42.3)	79 (49.7)	

Abbreviations: BMI, body mass index; DMPA, depot medroxyprogesterone acetate.

\*Data are given as number (percentage) of subjects or mean ± SD.

† $\chi^2$  Tests or analyses of variance, as appropriate.

‡Self-description of physical activity level from a selection of 3 choices: inactive, normal, active.

**Table 2. Mean Weight Increase\* From Baseline to 18 Months According to Contraceptive Method**

Contraceptive Method	Nonobese	Obese	Tukey-Kramer Adjusted P Value Within Group
DMPA	4.04 (0.44)	9.45 (1.05)	<.001
Oral contraceptive	2.81 (0.43)	0.16 (0.64)	.007
Control	3.50 (0.35)	3.07 (0.75)	.99

Abbreviation: DMPA, depot medroxyprogesterone acetate.

\*Adjusted by means of analysis of variance for race, gynecologic age, and previous pregnancy. Sample stratified according to baseline obesity status (nonobese, body mass index <30; obese, body mass index ≥30). Data are given as mean (SE) weight in kilograms.

## RESULTS

Baseline characteristics according to contraceptive method are shown in **Table 1**. There was a significantly greater percentage of obese subjects in the OC group than in the DMPA or control group. As a result, baseline weight and BMI were greater for the OC group. Stratification according to baseline obesity status resolved differences in baseline weight and BMI across contraceptive methods. The control group was significantly younger than the DMPA and OC groups at baseline according to chronological and gynecologic age. The DMPA group had a significantly higher rate of previous pregnancy compared with rates in the OC and control groups. No differences were seen across contraceptive methods in racial distribution, reported regular menses, or physical activity level.

At 18 months, study withdrawal rates according to contraceptive method were as follows: DMPA, 37.4% (43/115); OC, 46.3% (81/175); and control, 25.0% (40/160). As previously described, appointment non-

compliance, medication noncompliance, withdrawn study consent, change of contraceptive method, use of non-permitted contraception, and positive pregnancy test constituted the major reasons for study withdrawal. During the study, 17 (9.7%) of 175 subjects receiving OC, 3 (1.9%) of 160 control subjects, and 0 (0%) of 115 subjects receiving DMPA became pregnant.

Mean weight change, adjusted for race, gynecologic age, and previous pregnancy, from baseline to 18 months is demonstrated in **Table 2** according to contraceptive method and obesity status. Over the 18 months, non-obese subjects receiving DMPA, OC, or no hormonal method had mean weight changes of 4.0, 2.8, and 3.5 kg, respectively. Among obese subjects, those receiving DMPA, those receiving OC, and control had mean weight changes of 9.4, 0.2, and 3.1 kg, respectively. Weight gain in obese girls receiving DMPA was significantly greater than weight gain in obese girls receiving OC ( $P < .001$ ) and obese girls using no hormonal method ( $P < .001$ ). Weight gain in obese girls receiving DMPA was also greater than weight gain in all nonobese categories ( $P < .001$ ). Nonobese subjects receiving OC gained significantly more weight than did obese subjects receiving OC ( $P = .007$ ). In analysis of variance modeling, a significant interaction between baseline obesity status and contraceptive method ( $P < .001$ ) was evident; adolescent girls who initiated DMPA were more likely to gain weight over time than those who initiated OC or no method, and this weight gain was accentuated by being obese at baseline.

**Table 3** shows incidence of obesity at 6, 12, and 18 months, according to contraceptive method, for subjects who were nonobese at baseline (ie, the percentage of nonobese subjects who became obese at each time point). Among nonobese subjects, 8 (19.0%) of 42 receiving DMPA, 4 (9.8%) of 41 receiving OC, and 2 (2.8%) of 71 control subjects became obese by 18 months.

Repeated-measures adjusted mean weight stratified according to baseline obesity status is shown in **Table 4**. For nonobese subjects, contraceptive method was not significantly associated with weight ( $P = .31$ ). Predictors of weight for nonobese subjects included black race ( $P = .003$ ), younger gynecologic age ( $P = .002$ ), and length of time in study ( $P < .001$ ). Conversely, perhaps because of smaller sample sizes and thus less power, race ( $P = .82$ ) and gynecologic age ( $P = .40$ ) were not predictive of weight for obese subjects. A significant interaction was seen, however, between contraceptive method and length of time in study ( $P = .006$ ). This interaction effect suggests that, during the 18-month observation period, DMPA use among obese subjects was associated with an increasing rate of weight gain with longer duration of use.

### COMMENT

In this 18-month prospective study of adolescent girls initiating DMPA, OC, or no hormonal contraceptive method, we found a significant relationship between baseline obesity status and subsequent weight gain. Adolescent girls who were obese at initiation of DMPA gained significantly more weight than obese girls starting OC or no contraceptive method. In addition, obese adolescents receiving DMPA gained more weight than did nonobese adolescents using DMPA, OC, or no hormonal contraceptive method (control).

Among nonobese adolescents, we found no statistically significant effect of contraceptive method on weight. However, weight gain was greatest among nonobese subjects receiving DMPA, averaging 4.0 kg at 18 months. This amount of weight gain is not inconsequential and could be cause for concern in populations vulnerable to obesity.

Furthermore, weight gain in nonobese subjects receiving OC was significantly greater than in obese subjects receiving OC. Evidence suggests that hormonal steroid kinetics may contribute to differing clinical outcomes between obese and nonobese women receiving OC. A small study of ethinyl estradiol plasma concentrations in women receiving OC showed a negative correlation between ethinyl estradiol levels and body weight.<sup>12</sup> Women in the lowest plasma ethinyl estradiol quartile had a nonsignificant but greater mean weight than those in the highest quartile (64.0 vs 60.1 kg). However, women of extreme body weight were not included in this study. Recent evidence also demonstrates that greater body weight is associated with an increased risk of OC failure.<sup>13,14</sup> Among consistent OC users, the risk of pregnancy is more than 70% higher in women weighing more than 74.8 kg and nearly double in women weighing more than 86.2 kg.<sup>14</sup> The risk of OC failure increases among overweight women as the OC estrogen dose decreases.<sup>13</sup> Taken together, the results of these studies seem to suggest that lower circulating ethinyl estradiol levels may be present in obese women receiving OC compared with their nonobese peers. In the present study, less weight gain among obese subjects perhaps also reflects lower circulating contraceptive concentrations in this group.

**Table 3. Incidence of Obesity Among Subjects Nonobese at Baseline and at 6, 12, and 18 Months According to Contraceptive Method**

Contraceptive Method	No. Who Became Obese/ No. Who Remained Obese, %		
	6 Months	12 Months	18 Months
DMPA (100 nonobese at baseline)	4/87 (4.6)	6/62 (9.7)	8/42 (19.0)
Oral contraceptive (124 nonobese at baseline)	6/93 (6.5)	7/64 (10.9)	4/41 (9.8)
Control (132 nonobese at baseline)	4/120 (3.3)	4/97 (4.1)	2/71 (2.8)

Abbreviation: DMPA, depot medroxyprogesterone acetate.

Among adolescents who were nonobese at baseline, incidence of obesity was highest in those receiving hormonal contraception. At 18 months, incidence of obesity was 19.0% and 9.8% for nonobese subjects receiving DMPA and OC, respectively, compared with 2.8% for control subjects.

An estimated 10%, or approximately 1 million, adolescent girls aged 15 to 19 years use DMPA as their contraceptive method.<sup>15,16</sup> With the ever-increasing prevalence of obesity, ranging from 12.4% (28/226) to 26.6% (81/304) of adolescent girls depending on racial background,<sup>17</sup> the number of obese adolescents possibly choosing DMPA is potentially large. Because obese adolescents receiving OC did not gain weight, one may conclude that OC is the best contraceptive option for an obese adolescent. However, although OC use in obese adolescents was not associated with adverse effects on weight gain in this study, method discontinuation rates were markedly higher among those receiving OC compared with those receiving DMPA: 46.3% vs 37.4%, respectively. Furthermore, the pregnancy rate among adolescents receiving OC was 10%, whereas no subjects receiving DMPA became pregnant. As previously noted, new evidence also suggests that women with elevated body weight may be at greater risk for OC failure, even with good method compliance.<sup>13,14</sup> Unintended pregnancy in adolescence, in addition to its own effect on weight, has enormous adverse social and financial consequences. Therefore, is continued weight gain or pregnancy a larger burden for an obese adolescent?

The reasons for an interaction between obesity status and DMPA-associated weight gain are unclear. Earlier research showed a glucocorticoid agonist activity of DMPA<sup>18</sup> and DMPA interference with insulin action<sup>19</sup> and serotonin metabolism.<sup>20</sup> Interactions between obesity status and such DMPA mechanisms should be explored in future studies. Furthermore, interindividual variability in DMPA pharmacokinetic measures has been documented. Wide interindividual variability has been seen in serum medroxyprogesterone acetate levels at the end of the 3-month injection period<sup>21,22</sup> and in the time needed for resumption of ovulation after using DMPA.<sup>23,24</sup> Although the possible influence of weight, BMI, and race on medroxyprogesterone acetate levels has been investigated,<sup>22,23,25</sup> overall, few studies have done so, and the

**Table 4. Mean Weight\* at Baseline and at 6, 12, and 18 Months According to Contraceptive Method**

Contraceptive Method	Baseline	6 Months	12 Months	18 Months
Nonobese subjects†				
DMPA	57.66 (1.08)	58.07 (1.09)	59.51 (1.15)	62.05 (1.26)
Oral contraceptive	59.40 (0.98)	60.40 (1.01)	61.39 (1.08)	62.65 (1.21)
Control	57.53 (0.94)	58.94 (0.95)	59.59 (0.98)	60.74 (1.04)
Obese subjects‡				
DMPA	91.61 (3.02)	96.47 (3.09)	99.71 (3.12)	101.02 (3.39)
Oral contraceptive	91.39 (1.75)	91.40 (1.80)	90.82 (1.88)	90.10 (2.02)
Control	91.44 (2.35)	94.05 (2.39)	94.21 (2.44)	93.50 (2.61)

Abbreviation: DMPA, depot medroxyprogesterone acetate.

\*Adjusted by means of repeated-measures analysis of variance for race, gynecologic age, and previous pregnancy. Sample stratified according to baseline obesity status (nonobese, body mass index <30; obese, body mass index ≥30). Data are given as mean (SE) weight in kilograms.

†Significant ( $P < .001$ ) increases in weight, for all nonobese groups, across time. No difference according to contraceptive method.

‡Significant ( $P = .006$ ) interaction between DMPA use and time using method in obese adolescent girls.

methodologies of some studies are unclear, suggesting a need for further investigation.

Limitations of the present study must be considered. The present study represents an analysis of secondary data from a study designed to evaluate hormonal contraception and bone mineral density in adolescents. Furthermore, subjects selected their contraceptive method rather than being randomly assigned one. Although random assignment of treatment groups would be preferable, random assignment of contraceptive method would not be ethical. In clinical practice, a variety of patient factors, including perceived ease of use, perceived adverse effects, and personal preference, affect contraceptive choice. All these variables can affect patient satisfaction and compliance with a contraceptive method. Because pregnancy is an undesirable outcome with contraception use and method compliance tends to be poor in adolescents, patient preference must dictate contraceptive choice to maximize adherence. We acknowledge that this may introduce inherent bias in the study sample as demonstrated by differences between the control subjects and adolescents receiving DMPA and OC. Although not different in racial composition and recruited from the same clinical sites as subjects receiving DMPA and OC, control subjects were significantly younger. Of note, rate of growth, and, hence, rate of weight gain, is highest in girls during the earlier phases of puberty and, hence, highest among adolescent girls of younger gynecologic age, so greater weight gain would be expected rather than lower weight gain among the younger control group.

Generalizability of the present study results also must be considered. The study sample was primarily black urban adolescents. The study findings may not be applicable to populations of other racial backgrounds or adult women.

In conclusion, to our knowledge, our study is the first to follow up and compare prospectively weight changes in a large cohort of obese and nonobese adolescent girls initiating hormonal contraception and control subjects not receiving hormonal contraception. Our study demonstrates a relationship between contraceptive weight gain and obesity; DMPA use dramatically increased rates of

weight gain in obese subjects. In BMI units, the effect of the 9-kg weight gain in obese adolescents receiving DMPA is 3 in an adolescent of average height. With an estimated 150 000 obese adolescents using DMPA as a contraceptive method,<sup>15-17</sup> the potential contribution of DMPA to severe obesity is concerning. Significant weight gains were not observed in obese subjects receiving OC. One might conclude, therefore, that OC is the best contraceptive choice in the obese adolescent. However, with previous research documenting poor compliance and high rates of pregnancy in adolescents receiving OC, the best choice of contraception for obese teenagers is unclear, highlighting the need for further research in this area.

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### Announcement

**Helping the Student With Diabetes Succeed: A Guide for School Personnel Now Available From the National Diabetes Education Program.** This comprehensive guide provides school personnel, parents, and students with a framework for managing diabetes effectively in the school setting. The guide helps to ensure that students with diabetes are medically safe and have access to all educational opportunities and activities. Developed by the US Department of Health and Human Services' National Diabetes Education Program, the guide includes user-friendly tools such as a diabetes primer and glossary, sample medical management and emergency action plans, and a review of federal laws pertaining to students with diabetes. To obtain a free copy of the guide, call 1-800-438-5383 or visit the National Diabetes Education Program Web site at <http://ndep.nih.gov/diabetes/youth/youth.htm>.