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Early Weight Gain Related to Later Weight Gain in Adolescents on Depot Medroxyprogesterone Acetate

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Abstract

Objective—To examine if early weight gain in adolescents on depot medroxyprogesterone acetate (DMPA) predicts continued excessive weight gain and identify risk factors of early weight gain.

Methods—Adolescents (N=97) initiating DMPA were eligible to participate. Height and weight were assessed at baseline, 6, 12, and 18 months. Early weight gain was defined as more than a 5% weight gain after 6 months of DMPA use. Mean body mass index (BMI) at 6-month intervals was estimated based on early weight gain status (less than or equal to 5% gain vs. greater than 5% gain). Analysis of variance (ANOVA) modeling was used to compare group BMI at each time point. Repeated measures analysis of co-variance (ANCOVA) modeling was used to explore the association between early weight gain and percentage change in BMI at 12 and 18 months of DMPA use.

Results—Twenty patients (21%) had early weight gain. Mean BMI (kg/m²) for the 5% or less group and greater than 5% group was 23.4 and 24.5 ($p=.31$), 23.3 and 26.6 ($p=.009$), 24.2 and 28.7 ($p=.007$), and 25.7 and 32.1 ($p=.01$) at 0, 6, 12, and 18 months, respectively. Early weight gain was significantly associated with percentage change in BMI at 12 and 18 months ($p < .001$). No risk factors for early weight gain were identified.

Conclusion—Adolescents who experience more than 5% weight gain after 6 months of DMPA use are at risk for continued excessive weight gain. Weight gain after 6 months on DMPA can be used to identify adolescents at risk for continued weight gain, and appropriate counseling can be done at this time point.

Introduction

Depot medroxyprogesterone acetate (DMPA) has many features that are clinically appealing for use in adolescents. It is extremely effective (less than 1% annual failure rate), obviates the need for daily or weekly compliance, and can be used privately (1). Despite its unique features and strengths, DMPA use among adolescents continues to be hindered by concerns about weight gain. Weight gain has been reported in up to 54% of adolescents receiving

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DMPA and is cited as the primary reason for method discontinuation by 41% of adolescents who use this method (2;3).

Weight gain on DMPA is highly variable (4). Reported mean weight gain after 1 year of DMPA use ranges from 0.05 to 4.44 kg (5;6). Predicting which patients will experience substantial weight gain on DMPA can be difficult. Studies examining risk factors for weight gain among adolescents on DMPA suggest that black racial background and overweight status are independent risk factors (7-10). However, the strength of these findings at this time point is not sufficient to preclude African American or obese adolescents from using this contraceptive method. Among adult women on DMPA, African American race was also found to be a risk factor for weight gain; however, baseline obesity was found to be protective, suggesting that age may affect the clinical usefulness of these predictors (11).

Recently Le and colleagues reported that among women age 16 – 33 years, women who experience > 5% body weight increase within 6 months of DMPA use were at risk for future weight gain with continued DMPA use (11). Whether early weight gain status is predictive of continued weight gain on DMPA among younger users is not known.

The primary objective of the current study was to examine if early weight gain, similarly defined as more than a 5% increase in body weight within 6 months of DMPA use, predicts continued excessive weight gain on DMPA among adolescents age 12 – 18 years. Furthermore, we explored predictors of early weight gain at 6 months of DMPA use.

Materials and Methods

The present study represents a secondary analysis of data collected from May 2000 through January 2003 on a cohort (N = 433) of adolescent girls who enrolled in a 2-year study of hormonal contraception and bone mineral density. Detail study methods have been previously reported (12;13). The study population consisted of post-menarcheal girls, age 12 – 18 years, attending one of four urban adolescent health clinics in a large metropolitan area. Adolescent girls requesting contraception, and selecting either DMPA or OC, were eligible to participate. In addition, adolescent girls who planned to receive no hormonal contraception were eligible for enrollment as control subjects. One major aim of the parent study was to evaluate whether estrogen supplementation in subjects receiving DMPA resulted in decreased BMD losses. As such, DMPA subjects were randomized to receive either monthly injections of 5mg estradiol cypionate or placebo. The current analyses include only those subjects selecting DMPA for contraception (N = 97), both those randomized to receive estradiol cypionate or placebo.

Exclusion criteria for study participation included pregnancy or DMPA use within the preceding 6 months; OC use within the preceding 3 months; alcohol or drug dependence; medical condition (e.g. renal disease) or medication use (e.g. corticosteroids) known to be associated with the outcomes of interest; contraindication to estrogen use; weight exceeding 250 lbs (upper limit for DEXA scanner); and need for confidential contraceptive care. 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 approved by the institutional review board of the participating institutions.

At baseline, 6, 12, 18, months, clinical and behavioral information was obtained from each study participant. Height and weight were measured by using the same stadiometer (Easy Glide Bearing stature board) and Mettler-Toledo scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Gynecologic

age was calculated as the number of years since menarche. Physical activity was assessed with a survey that asked each participant to classify herself as inactive, normal, or active.

Since Le and colleagues found that early weight gain, defined as more than 5% weight gain at 6 months of DMPA, was most predictive of continued weight gain in adult women (11), we dichotomized our DMPA users into those who did or did not experience a > 5% increase in body weight at 6 months of DMPA use. Girls who experienced more than a 5% weight gain at 6 months were classified as “early weight gainers” and girls who experienced less than or equal to a 5% weight gain at 6 months were classified as “non-early weight gainers.” In our study, group comparisons at baseline were completed using chi-square tests or Fisher's exact tests, as appropriate, for categorical variables and t-tests or Wilcoxon rank sum tests, as appropriate, for continuous variables. One-way Analysis of Variance (ANOVA) modeling was used to compare groups at each of the times points (baseline, 6 months, 12 months, 18 months) on BMI. Using BMI ≥ 85 th and < 95 th sex- and age-specific percentile from the 2000 CDC growth charts as the definition of overweight and BMI ≥ 95 th sex- and age-specific percentile from the 2000 CDC growth charts as the definition of obese, we calculated the percentage of both early and non-early weight gainers who were overweight or obese at each time point.

Repeated measures ANCOVA modeling was then used to explore the association between early weight gain and the percentage change in BMI after 12 and 18 months of DMPA use. In the repeated measures ANCOVA modeling, we incorporated a factor for group and time, while adjusting for possible baseline characteristics (age, gynecologic age, race, ethnicity, BMI, menstrual regularity, duration of menses, menstrual cycle length, sexual activity, previous pregnancy, physical activity, and randomization to estradiol or placebo). Results with p-value less than or equal to an alpha-level of 0.05 were considered statistically significant. Data analyses were conducted with SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Of the 97 adolescents who selected DMPA, 20 (21%) increased their weight by more than 5% at 6 months. A comparison of baseline characteristics between subjects who did or did not experience early weight gain is shown in Table 1. There was no difference between the two groups in age, menarcheal age, gynecologic age, race, ethnicity, weight, height, BMI, menstrual regularity, duration of menstrual flow, length of menstrual cycle, prevalence of sexual activity, previous pregnancy or reported physical activity. In addition, there was no association between randomization to estradiol or placebo and early weight gain status.

BMI at baseline, 6, 12, and 18 months based on early weight gain status is demonstrated in Table 2. Although not different at baseline, mean BMI, for subjects who experienced > 5% increase in body weight after 6 months of DMPA use as compared to those who did not, was significantly ($p < .01$) higher at 6, 12 and 18 months; mean BMI (kg/m^2) at baseline was 24.5 (early gainers) vs. 23.4 (non-early gainers); mean BMI at 6 months was 26.6 (early gainers) vs. 23.3 (non-early gainers); mean BMI at 12 months was 28.7 (early gainers) vs. 24.2 (non-early gainers); mean BMI at 18 months was 32.1 (early gainers) vs. 25.7 (non-early gainers). Over 18 months, early weight gainers experienced an increase in mean BMI of 7.6 as compared to 2.3 for non-early weight gainers. Of note, as indicated by the range of BMI at baseline for both early and non-early weight gainers, the subject with the highest baseline BMI were found in the non-early weight gain group.

At baseline, 40% of early weight gainers and 35% of non-early weight gainers were either overweight or obese. At 6 months, 60% of early weight gainers and 29% of non-early

weight gainers were either overweight or obese. By 12 and 18 months respectively, 75% and then 86% of early weight gainers met the criteria for overweight or obese. In contrast, 37% and then 52% of non-early weight gainers met criteria for overweight or obese at 12 and 18 months.

Repeated measures ANCOVA modeling the association between early weight gain group and percentage change in BMI at 12 and 18 months is shown in Table 3. Early weight gain was significantly associated with percentage change in BMI at both 12 and 18 months of continued DMPA use ($p < .001$). Study visit was also significantly associated with percentage change in BMI at 12 and 18 months indicating that subjects gained weight over time. The interaction between time and weight gain group was evaluated and was not significant. In addition, no baseline characteristics were associated with percentage change in BMI at 12 or 18 months.

All baseline characteristics were also examined for association with early weight gain group. No risk factors for early weight gain were found including: age; menarcheal age; gynecologic age, race; ethnicity; baseline weight; baseline BMI; menstrual regularity; menstrual cycle length; duration of menses; sexual activity; physical activity; or randomization to estradiol or placebo.

Discussion

Similar to Le and colleagues' study among adult women (11), the current study found that adolescents who gained $> 5\%$ of their baseline weight at 6 months of DMPA use were much more likely to continue gaining a significant amount of weight over the next 12 months with continued DMPA use. Subjects with early weight gain experienced a mean increase in BMI of 7.6 kg/m^2 over 18 months. Whereas 40% of early weight gainers were overweight or obese when starting DMPA, 85% were overweight or obese at 18 months. The longitudinal nature, large sample size, and consistency of findings between the current study and that of Le and colleagues suggest that weight gain status at 6 months is robust predictor of excessive weight gain on DMPA among adolescent and young women up to 33 years of age.

In our study, 21% of subjects experienced early weight gain. This finding adds to the growing literature demonstrating that weight gain on DMPA is not a uniform finding for all patients (4;10;11). In fact, 3 out of 4 patients did not experience significant weight gain within the first 6 months of DMPA use. Although the percentage of non-early weight gainers who were either overweight or obese rose from 37% to 52% between 12 and 18 months, the percentage remained stable during the first year on DMPA. Whether this late rise in the prevalence of overweight or obese among non-early weight gainers is a real or spurious finding is not known. Given the typical short duration of use of DMPA by adolescents and the stable prevalence of percentage overweight or obese during the first year on DMPA, patients who experience $\leq 5\%$ weight gain at 6 months can likely be reassured regarding their future risk for weight gain. These patients should continue to receive routine diet and exercise counseling.

No demographic or clinical features were found to be predictive of early weight gain status in the current study. In contrast, Le et. al. identified four baseline risk factors for early weight gain: BMI < 30 ; parity > 1 ; self-reported increased appetite, and African American race. Our previous report on this data had found that baseline obesity was a risk factor for DMPA-associated weight gain at 6, 12, and 18 months (10). This report, however, did not include early weight gain, i.e. weight gain at 6 months on DMPA, in the analyses models. With the incorporation of early weight gain, we now find early weight gain to be a more powerful predictor than baseline obesity of later weight gain on DMPA. The suggestion of

these findings is that regardless of baseline characteristics, i.e. African American race or obesity, if > 5% weight gain has not occurred at 6 months on DMPA, the risk for future weight gain is reduced.

Several sources of bias are present in our study. Since study subjects self-selected contraceptive method, rather than being randomized into treatment groups, confounding influences on the relationship between body weight and contraceptive method may be unevenly distributed among treatment groups. In addition, study attrition rate may also have impacted study results. However, no significant differences were identified between subjects who did or did not finish the study, so we do not think this was a source of bias.

In summary, a subset of adolescents on DMPA experiences a significant amount of weight gain on this contraceptive method. Adolescents who have > 5% increase in body weight after 6 months of DMPA use are at increased risk for continued excessive weight gain which could have negative health consequences for this population. Weight gain, however, is not a uniform finding among all adolescents on DMPA. In fact, the majority of adolescent users do not experience extreme weight gain on this method. Our study further supports that weight gain after 6 months of DMPA is a useful clinical tool to identify those at risk for continued weight gain and appropriate contraceptive counseling can be done at this time point.

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Table 1
Subject characteristics at baseline based on weight gain status at 6 months of DMPA use

Characteristic	Statistic	≤ 5% Weight Gain at 6 Months (n=77)	> 5% Weight Gain at 6 Months (n=20)	P-value
Age (yrs)	Mean ± SD	15.7 ± 1.4	16.1 ± 1.5	0.31
	Range	12.6 to 19.0	14.0 to 18.4	
	Median	15.5	16.0	
Menarcheal Age (yrs)	Mean ± SD	12.0 ± 1.6	12.0 ± 1.2	0.92
	Range	8.5 to 16.1	9.9 to 14.9	
	Median	12.2	11.9	
Gynecologic Age (yrs)	Mean ± SD	3.7 ± 1.7	4.1 ± 1.7	0.35
	Range	0.2 to 8.1	0.7 to 6.9	
	Median	3.7	4.1	
Race (n, %)	Black	49 (63.6)	13 (65.0)	0.99
	White	26 (33.8)	7 (35.0)	
	Other	2 (2.6)	0 (0.0)	
Ethnicity (n, %)	Hispanic Non-	4 (5.2)	0 (0.0)	0.58
	Hispanic	73 (94.8)	20 (100.0)	
Weight (kg)	Mean ± SD	61.1 ± 13.6	65.0 ± 17.2	0.29
	Range	39.0 to 109.0	45.0 to 96.0	
	Median	59.0	57.5	
Height (cm)	Mean ± SD	161.5 ± 6.9	161.7 ± 7.2	0.95
	Range	145.0 to 175.0	151.0 to 173.0	
	Median	163.0	160.0	
BMI (kg/m ²)	Mean ± SD	23.4 ± 4.6	24.5 ± 4.5	0.31
	Range	16.3 to 39.8	18.3 to 32.1	
	Median	22.2	23.8	
Menses (n, %)	Regular	64 (83.1)	18 (90.0)	0.73
	Irregular	13 (16.9)	2 (10.0)	
Duration of menstrual flow (days)	Mean ± SD	5.1 ± 1.6	5.2 ± 1.1	0.77
	Range	0.0 to 9.0	4.0 to 7.0	
	Median	5.0	5.0	
Length of menstrual cycle (days)	Mean ± SD	28.3 ± 6.0	29.1 ± 2.2	0.10
	Range	0.0 to 55.0	21.0 to 31.0	
	Median	28.0	30.0	
Sexually Active (n, %)	Yes	58 (75.3)	13 (65.0)	0.99
	No	16 (20.8)	4 (20.0)	

Characteristic	Statistic	$\leq 5\%$ Weight Gain at 6 Months (n=77)	$> 5\%$ Weight Gain at 6 Months (n=20)	P-value
	Unknown	3 (3.9)	3 (15.0)	
Previous Pregnancy (n, %)	No	75 (97.4)	18 (90.0)	0.19
	Yes	2 (2.6)	2 (10.0)	
Physical Activity (n, %)	Active	25 (32.5)	9 (45.0)	0.51
	Normal	43 (55.8)	10 (50.0)	
	Inactive	9 (11.7)	1 (5.0)	
Randomization (n, %)	Estradiol	38 (49.4)	10 (50.0)	0.96
	Placebo	39 (50.6)	10 (50.0)	

Table 2
Body mass index (BMI) at 0, 6, 12, and 18 months by weight gain status after 6 months of DMPA use

BMI (kg/m ²)	Statistic	≤ 5% Weight Gain at 6 Months	> 5% Weight Gain at 6 Months	P-value
0 months	Mean ± SD	23.4 ± 4.6	24.5 ± 4.5	0.31
	Median	22.2	23.8	
	Range	16.3-39.8	18.3-32.1	
6 months	Mean ± SD	23.3 ± 5.0	26.6 ± 5.1	0.009
	Median	21.5	25.9	
	Range	16.3-40.2	19.6-35.3	
12 months	Mean ± SD	24.2 ± 5.5	28.7 ± 5.6	0.007
	Median	22.5	28.5	
	Range	17.2-41.5	20.4-37.8	
18 months	Mean ± SD	25.7 ± 6.0	32.1 ± 5.7	0.01
	Median	24.0	30.5	
	Range	18.4-41.8	23.3-37.9	

Table 3
Repeated measures analysis of covariance^a modeling the association between early weight gain^b and percentage change in body mass index (BMI) after 12 and 18 months of DMPA use

Factor	P-value	Mean (SD)
Early Weight Gain	<0.001	No vs. Yes 3.7% (0.9%) vs. 14.7% (1.9%)
Visit Month	0.03	12 vs. 18 7.3% (1.2%) vs. 11.0% (1.5%)

^a Eligible co-variables included age, gynecologic age, race, ethnicity, BMI, menstrual regularity, duration of menses, menstrual cycle length, sexual activity, previous pregnancy, physical activity, randomization to estradiol or placebo, and time by group interaction.

^b Early weight gain defined as: No = gained $\leq$ 5% of baseline weight at 6 months of DMPA use; Yes = gained $>$ 5% of baseline weight at 6 months of DMPA use.