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Original Research

Depot Medroxyprogesterone Acetate Use and the Development and Progression of Uterine Leiomyoma

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OBJECTIVE: Investigate the association between use of depot medroxyprogesterone acetate (DMPA) (an injectable progestin-only contraceptive) and leiomyoma development.

METHODS: We conducted a cohort study in the Detroit, Michigan, area that involved four clinic visits at 20-month intervals over 5 years (2010–2018) and used a standardized ultrasonography protocol to prospectively measure leiomyomas 0.5 cm or more in diameter. Participants were 1,693 self-identified Black women aged 23–35 years with no prior leiomyoma diagnosis and no hysterectomy. For this substudy, years since last use of DMPA was ascertained from questionnaire data at every visit. *Leiomyoma incidence* was defined as the first visit with an observed leiomyoma among women who were leiomyoma-free at enrollment. Depot medroxyprogesterone acetate associations were examined with Cox models. *Leiomyoma growth* was calculated as the change in log-volume for leiomyomas matched at successive visits and was modeled using linear mixed models accounting for clustered data. *Leiomyoma loss*, defined as a reduction in leiomyoma number in successive visits, was modeled using Poisson regression. All models used time-varying exposure and covariates.

RESULTS: Of participants with at least one follow-up visit (N=1,610), 42.9% had ever used DMPA. Participants exposed to DMPA within the previous 2 years experienced reduced leiomyoma development during the subsequent observation interval compared with never users, including lower leiomyoma incidence (5.2% vs 10.7%), adjusted hazard ratio 0.6 (95% CI 0.4–1.0), 42.0% lower leiomyoma growth (95% CI −51.4 to −30.7) and 60% greater leiomyoma loss (adjusted risk ratio 1.6, 95% CI 1.1–2.2). Excess leiomyoma loss was also seen for those who used DMPA 2–4 years before the visit compared with never users, 2.1-fold increase (95% CI 1.4–3.1).

CONCLUSION: Recent use of DMPA was associated with reduced leiomyoma development and increased leiomyoma loss. Such changes in early leiomyoma development in young women could delay symptom onset and reduce the need for invasive treatment.

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Uterine leiomyomas are nonmalignant tumors of the myometrium. Leiomyomas develop in up to 80% of women[1] and can cause debilitating symptoms including heavy menstrual bleeding, anemia, and pel-

vic pain.[1] These tumors are the leading indication for hysterectomy in the United States[2] and other countries.[3–5] Medical and surgical treatment of leiomyomas can have adverse effects, may be at odds with childbearing goals, and leiomyomas may return after nonhysterectomy treatment.[6] The identification of factors that may either reduce incidence or slow growth is vital to reducing the burden of this condition.

To date, few modifiable risk factors for leiomyomas have been identified,[7] and nearly all studies have relied on comparisons between women with and without clinically identified leiomyomas. Without standardized screening, as is typical for breast and cervical cancer, however, clinical diagnosis of leiomyomas will be dependent on symptomatology and access to care. As a result, many such "incident cases" will have had leiomyomas for years before diagnosis and many "noncases" will have leiomyomas that are not yet diagnosed. Longitudinal studies using ultrasonographic screening of a nonclinical population are needed for better ascertainment of factors associated with leiomyoma incidence and growth.

A factor with some prior evidence for reducing leiomyoma burden is depot medroxyprogesterone acetate (DMPA [Depo-Provera]), a long-acting, progestin-only injectable contraceptive.[8–10] However, the prior findings could have resulted from reverse causation or selection bias if DMPA was prescribed to treat symptoms of leiomyomas or if DMPA for contraception suppressed symptoms, delaying clinical diagnosis. In the current study, we conducted prospective standardized ultrasonographic screening over 5 years in a community sample of young women and examined the associations of DMPA use with leiomyoma incidence and growth.

METHODS

SELF (the Study of Environment, Lifestyle & Fibroids) is a prospective cohort study of leiomyoma incidence and growth[11] with collection of a broad range of exposures, not limited to the primary factors of interest: reproductive-tract infections, vitamin D insufficiency and genetic ancestry. Given the higher leiomyoma burden and 10-year earlier age of onset for Black women compared with White women in the United States,[12] SELF enrollment was restricted to Black women. Participants self-identified the social construct of race by answering "yes" or "no" to "Black or African American" among a list of racial and ethnic categories. SELF recruited participants from the Detroit, Michigan area from 2010 to 2012 in collaboration with the Henry Ford Health System. Full recruitment and eligibility criteria have been previously described[11] (Appendix 1, available online at http://links.lww.com/AOG/C671). Primary eligibility criteria were age 23 to 35 years, premenopausal, and no clinical diagnosis of leiomyomas. Enrolled participants completed all baseline activities including the first study ultrasonogram.

SELF enrolled 1,693 participants. After the enrollment visit, participants returned approximately every 20 months for a total of four visits. Study visits ended in 2018. Visits included collection of data using questionnaires, interviews, and a clinical visit for ultrasonographic examination and measurement of weight and height. Visits were delayed for pregnant participants until 3–4 months postpregnancy. Active engagement of participants through newsletters and an excellent study staff, resulted in a high retention rate. Participants who missed a follow-up were invited to the next follow-up. At the final study visit (visit 4), 91% completed data collection. Over the course of the study, 95% attended at least two study visits and 79% attended all four study visits (Appendix 1, http://links.lww.com/AOG/C671). The current analysis includes data from 1,610 women with at least one completed ultrasonogram during follow-up, providing at least one interval between ultrasonographic examinations for analysis.

SELF was approved by the institutional review boards of the National Institute of Environmental Health Sciences and Henry Ford Health Systems. All participants provided written informed consent and received stipends.[11]

SELF was designed to investigate associations with the primary outcomes of leiomyoma incidence and growth. Experienced ultrasonographers followed a study protocol[11,13] for ultrasonographic examinations (Appendix 1, http://links.lww.com/AOG/C671) and were unaware of exposure status. Ultrasonography was conducted using a transvaginal approach, with the addition of a transabdominal approach if needed. The six largest leiomyomas 0.5 cm or more in any diameter were counted, localized, and measured, but most women had no more than two or three. Leiomyoma volume was calculated from three measured diameters using the ellipsoid formula and volumes from three separate passes through the uterus were averaged. Ultrasonographers noted problems with visualization (eg, calcifications, shadowing). Video and still images were archived, and an 8% sample for each ultrasonographer, oversampled for leiomyoma cases, was reviewed by the lead ultrasonographer (T.E.C.).

Incident leiomyoma cases were detected among women who were leiomyoma-free at baseline

(n=1,246). For analysis, visits with factors that impeded ultrasonographic visualization (eg, calcifications or shadowing, only a transabdominal ultrasonogram) were excluded (approximately 0.5% of ultrasonograms), resulting in incidence data for 1,232 participants (Fig. 1).

Leiomyoma growth (change in the natural logarithm of the tumor volume) was calculated for leiomyomas that could be matched across two successive visits. Matching individual leiomyomas across visits was completed by the lead ultrasonographer (T.E.C.) and one author (D.D.B.) based on archived images and leiomyoma location. Without a clear "match" at successive visits, a leiomyoma was considered "unmatched" and was not included in the analysis. No leiomyomas imaged after procedures such as myomectomy or uterine artery embolization were included. Change in volume was scaled to a growth rate per 18 months (median time between visits 19 months, 25th–75th percentile 18–21) by calculating daily growth rates and multiplying by 540. Growth data were also dichotomized into shrinking (decreasing volume) compared with nonshrinking leiomyomas. The growth analyses used data from 434 participants (n=1,359 interval growth measurements from successive visits).

We also analyzed leiomyoma loss, defined as a decrease in leiomyoma number between two successive visits. Accurate counts can be difficult when leiomyomas are numerous,[14] so this analysis was restricted to the 539 participants with at least two successive visits, four or fewer leiomyomas at the earlier

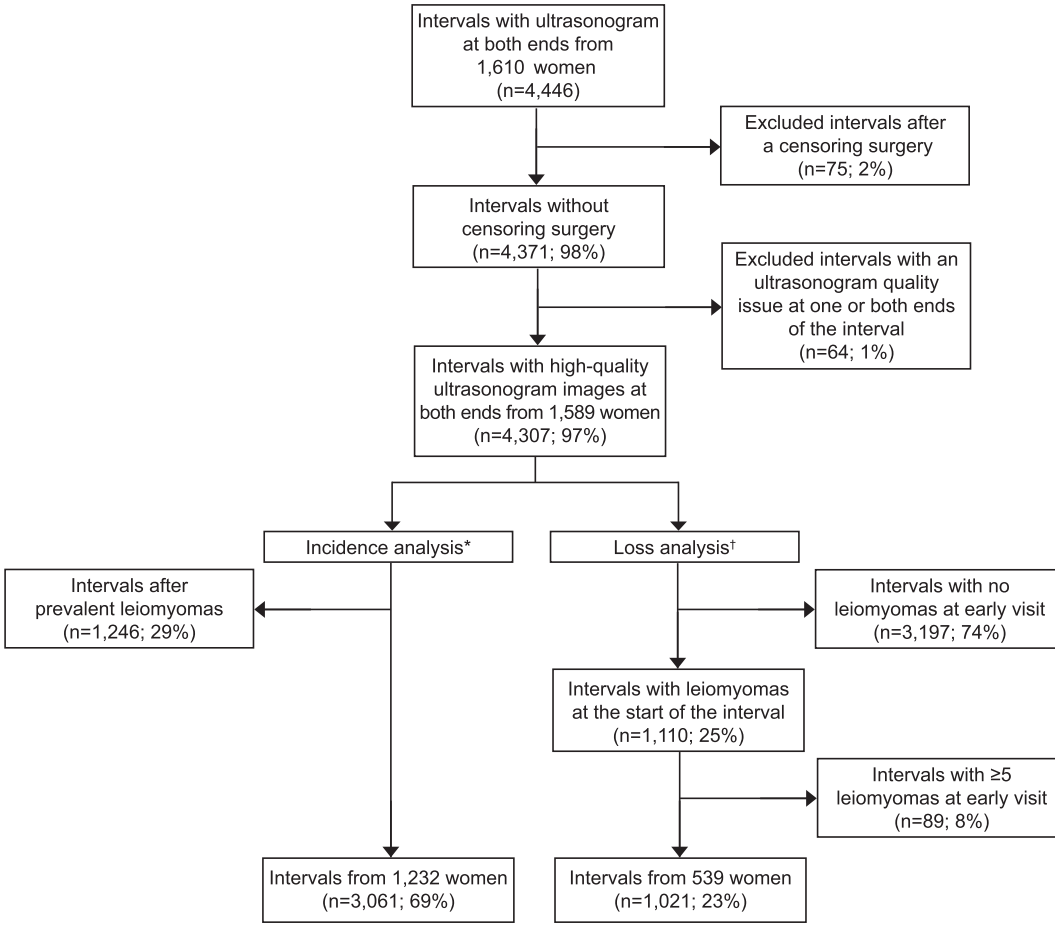

Fig. 1. Flow chart of intervals eligible for leiomyoma incidence and leiomyoma loss analyses. Percentages in exclusion boxes use eligible intervals in the preceding step as the denominator. Percentages in other boxes are based on 4,446 intervals. *Incidence analysis includes participants with no leiomyomas detected at baseline and with successive ultrasonograms meeting quality standards. †Loss analysis includes intervals with fewer than five leiomyomas at the start of the interval and successive ultrasonograms meeting quality standards. Loss analysis includes women from the incidence analysis after they develop a leiomyoma.

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visit, and no ultrasonographer report of impaired uterine visualization (Fig. 1). Intervals including or after a myomectomy, hysterectomy, or uterine artery embolization were also excluded. Leiomyoma loss includes shrinkage of leiomyomas below detection (0.5-cm diameter) and cannot be interpreted as completely resolved lesions.

At the enrollment visit, participants provided age at first and last use of DMPA and total lifetime months of use. At each follow-up visit participants reported any new or ongoing use of DMPA including months of use since the last study visit. At every visit we created an updated continuous measure of cumulative duration of use (months) up to the index visit and a variable for years since last use of DMPA. For women who used DMPA only before enrollment, we calculated the years since last use by subtracting age at last use from age at enrollment. For women who used DMPA during the study, we assigned age at last use at each follow-up visit based on the use of DMPA at the visit (current or past), months of use since the prior visit, and additional information on intervening pregnancies, postpartum use of DMPA, or use of other forms of hormonal contraceptives. When time since last use could not be identified with this information, the midpoint of the interval was assigned as the time of last use. For analysis, we categorized years since last use (0 to less than 2 years, 2 to less than 4 years, 4 to less than 8 years, 8 or more years) based on available sample size, aiming for more than 10 outcomes in every stratum. We updated the DMPA exposure variable and other time-varying factors at every visit.

These data on DMPA use did not allow us to accurately determine the duration of the most recent episode of use. Therefore, we focus on years since last use of DMPA. To confirm that observed associations were not restricted to participants with longer cumulative use, we conducted a secondary analysis. We modeled years since last use stratified by cumulative duration of use dichotomized into short-term (9 months or less) and long-term cumulative use (more than 9 months). We chose this cutpoint based on pharmacokinetic and contraceptive trial data for DMPA that show noncontraceptive changes, such as amenorrhea, are common after 9 months of use.[15]

The referent group for all analyses is Never Users of DMPA. Ever use of any form of hormonal contraceptives was common (86%) among SELF participants. At enrollment, ever use of estrogen-containing contraceptives was most frequent (81%)[16]; 43% of participants had ever used DMPA, and most participants in SELF (57%) had used multiple types of hormonal contraceptives. Given these patterns, the referent group includes participants who have only ever used non-DMPA hormonal contraceptives, as well as those who have never used any hormonal contraceptive. Current use of birth control pills, the other frequently used contraceptive, was explored as a potential confounder but was retained only for the leiomyoma growth outcome.

Because the literature on risk factors for leiomyomas is limited, we considered a wide range of covariates, and based final inclusions both on prior literature and evidence that the estimate for the DMPA exposure changed with adjustment for the covariate.[17] All covariates (except for age at menarche) were updated at each visit and were entered into models as time varying. Most were modeled categorically, using indicator variables, to allow for nonlinear associations (categories defined in the table footnotes); age and time between visits were continuous variables modeled as linear. Reproductive covariates considered were years since last birth, parity, age at menarche (ordinal), and current use of combined oral contraceptive. We estimated parity and years since last birth from the end of the interval between visits to incorporate events during the interval,[18] all other covariates were estimated at the beginning of the interval. Additional covariates considered were education, household income, current employment, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), and current smoking. For leiomyoma growth and loss models, leiomyoma volume and number of leiomyomas were included a priori based on prior work in this cohort.[19] Because minimal exposure and covariate data were missing (less than 0.5%), we anticipated minimal risk of selection bias and conducted complete case analyses.

Leiomyoma incidence associations with use of DMPA were modeled using a Cox regression, with age as the time scale to estimate hazard ratios and 95% CIs. Participants were included from age at enrollment until they had an incident leiomyoma detected at a study visit, non–leiomyoma-related hysterectomy, loss to follow-up, or the final study visit, whichever occurred first. The proportional hazards assumption was not violated based on a test of the interaction between DMPA exposure and age.

Leiomyoma growth was analyzed using linear mixed models to account for correlated growth among leiomyomas from the same woman and for the same leiomyoma over time as previously described[19,20] (Appendix 1, http://links.lww.com/AOG/C671). Plots of this estimated growth were constructed setting covariates at representative values.

For ease of interpretation, when comparing categories of DMPA exposure with never users we converted the model-based estimate of association (β) to an estimated percent difference in growth as $(\exp(\beta)-1)\times 100$ (Appendix 1, http://links.lww.com/AOG/C671). The relative risk of leiomyoma shrinkage for DMPA exposed compared with unexposed leiomyomas was estimated using a Poisson model accounting for repeated observations per woman. Leiomyoma loss was modeled using a Poisson regression model accounting for multiple observations per woman to estimate risk ratios and 95% CIs with robust standard errors.

We conducted six sets of sensitivity analyses to explore residual confounding, model assumptions (including timing of leiomyoma incidence within an interval and the influence of statistical outliers for growth), and how much growth results might be influenced by exposure-related differences in leiomyoma number and size. To rule out residual confounding due to unmeasured differences between women who use DMPA and women who do not, we inspected the estimates for women who used DMPA 8 or more years before a given visit, a remote exposure unlikely to affect our measures of leiomyoma development. All analyses used SAS 9.4 (Cary, NC) with two-tailed hypothesis testing and alpha 0.05.

RESULTS

At enrollment, participants had a mean age of 29±3.4 years, 78.0% had at least some college education, 62.2% were employed, and 45.1% had a household income less than $20,000. Almost a quarter of participants (23.9%) had BMIs of 40 or higher (Table 1). Almost half (42.9%) of participants had ever used DMPA; ever and never users of DMPA were generally similar to each other. Compared with never users, participants who had ever used DMPA at the baseline visit were more likely to have had a birth, have lower educational attainment and household income, and be current smokers (Table 1). Characteristics were similar for the participants in each leiomyoma outcome group (Appendix 2, available online at http://links.lww.com/AOG/C671), except that age and percent nulliparous, both known risk factors for leiomyoma prevalence, were higher in the subset of participants analyzed for growth and for leiomyoma loss. Participants had a median (25^{th}–75^{th} percentile) length of study participation of 4.8 years (4.7–5.0 years), with no difference by baseline DMPA exposure. Leiomyomas in this study, including undiagnosed leiomyomas detected at baseline and incident leiomyomas that developed during the study, were generally small. The median (25^{th}–75^{th} percentile) volume of leiomyomas followed for growth was 2.2 cm^3 (0.7–8.6 cm^3), and the median (25^{th}–75^{th} percentile) volume of incident leiomyomas was 0.7 cm^3 (0.25–1.8 cm^3). At enrollment, 22.7% of women had at least one leiomyoma (median 1, 75^{th} percentile 2); by the end of the study, 32.3% of women had leiomyomas (median 2, 75^{th} percentile 3).

Overall leiomyoma incidence between visits was 9.6%. In adjusted analyses, incidence differed little between ever and never DMPA users (Table 2); however, incidence did differ by years since last use. Recent use (within 2 years) was associated with reduced leiomyoma incidence (5.2%) compared with never users (10.7%), a 40% reduction in the adjusted risk of incident leiomyomas (adjusted hazard ratio [aHR] 0.6, 95% CI 0.4–1.0, P=.08) (Table 2).

Ever users of DMPA had marginally lower leiomyoma growth per 18 months than never users: an estimated 10.0% lower growth per 18 months (95% CI −18.4% to −0.8%) (Table 3). However, recent DMPA users (within 2 years of visit) had leiomyomas with markedly lower growth rates than never users (−42.0%, 95% CI −51.4% to −30.7%). In fact, for recent users, tumor growth had essentially stopped (0.3% change over 18 months, 95% CI −16.8 to 20.9%). This contrasts with never users whose leiomyomas increased an average of 72.8% in volume per 18 months (95% CI 55.5–92.1%) (Fig. 2 and Appendix 3 [Appendix 3 is available online at http://links.lww.com/AOG/C671]). Risk of shrinkage for leiomyomas exposed to DMPA within 2 years was twofold greater compared with never users (adjusted risk ratio [aRR] 2.0, 95% CI 1.4–2.9), with 40.4% (95% CI 28.0–58.4%) of leiomyomas in this DMPA exposure group showing shrinkage compared with 20.1% (95% CI 16.5–24.5%) of leiomyomas never exposed to DMPA (Appendix 4, available online at http://links.lww.com/AOG/C671).

Consistent with lower leiomyoma growth and higher leiomyoma shrinkage, those with ever DMPA use had a marginally higher crude leiomyoma loss (29.3%) compared with never users (21.6%) (Table 4). Those who used DMPA within 2 years or within 2–4 years of a visit had much higher estimated loss compared with never users: 60% (aRR 1.6, 95% CI 1.1–2.2) and an estimated 110% increased risk of loss (aRR 2.1, 95% CI 1.4–3.1), respectively.

In the secondary analysis that evaluated the role of cumulative duration of DMPA use we found that both short-term (9 months or less) and long-term (more than 9 months) users showed similar results for the time since last use analyses with the exception that

Table 1. Baseline Characteristics by Use of Depot Medroxyprogesterone Acetate: SELF (Study of Environment, Lifestyle & Fibroids) Cohort, Detroit, Michigan, 2010–2012

Characteristic	Overall	Never Used DMPA	Ever Used DMPA
Count	1,610 (100)	920 (57.1)	690 (42.9)
Study participation (y)	4.8 (4.7–5.0)	4.8 (4.7–5.0)	4.8 (4.7–5.0)
Age (y)			
23–25	356 (22.1)	231 (25.1)	125 (18.1)
26–28	407 (25.3)	236 (25.7)	171 (24.8)
29–31	439 (27.3)	231 (25.1)	208 (30.1)
32–35	408 (25.3)	222 (24.1)	186 (27.0)
Highest education			
High school or high school equivalency certificate or less	353 (21.9)	149 (16.2)	204 (29.6)
Some college, associate's degree, technical certificate	807 (50.2)	442 (48.0)	365 (53.0)
Bachelor's degree, master's degree, PhD	449 (27.9)	329 (35.8)	120 (17.4)
Missing	1	0	1
Annual household income ($)			
Less than 20,000	721 (45.1)	356 (38.9)	365 (53.4)
20,000–50,000	605 (37.9)	371 (40.6)	234 (34.2)
More than 50,000	272 (17.0)	187 (20.5)	85 (12.4)
Missing	12	6	6
Employment status			
On leave	3 (0.2)	1 (0.1)	2 (0.3)
Unemployed	605 (37.6)	295 (32.1)	310 (44.9)
Employed	1,002 (62.2)	624 (67.8)	378 (54.8)
BMI (kg/m^2)			
Lower than 25	318 (19.8)	178 (19.4)	140 (20.3)
25–29.9	331 (20.6)	174 (18.9)	157 (22.8)
30–34.9	310 (19.3)	190 (20.7)	120 (17.4)
35–39.9	267 (16.6)	155 (16.9)	112 (16.2)
40 or higher	384 (23.9)	223 (24.2)	161 (23.3)
Age at menarche (y)			
Younger than 11	297 (18.5)	159 (17.3)	138 (20.0)
11	325 (20.2)	191 (20.8)	134 (19.4)
12	430 (26.7)	261 (28.4)	169 (24.5)
13	274 (17.0)	165 (17.9)	109 (15.8)
Older than 13	284 (17.6)	144 (15.7)	140 (20.3)
Gravidity and parity			
Never pregnant	432 (26.8)	347 (37.7)	85 (12.3)
0 births	192 (11.9)	145 (15.8)	47 (6.8)
1–2 births	708 (44.0)	343 (37.3)	365 (52.9)
3 or more births	278 (17.3)	85 (9.2)	193 (28.0)
Years since last birth			
Within 3	363 (22.6)	170 (18.5)	193 (28.0)
3–4.9	207 (12.9)	88 (9.6)	119 (17.3)
5–9.9	289 (18.0)	120 (13.0)	169 (24.5)
10 or more	127 (7.9)	50 (5.4)	77 (11.2)
No birth	624 (38.8)	492 (53.5)	132 (19.1)
Current smoker			
Yes	310 (19.3)	149 (16.2)	161 (23.3)
Using OCP at visit			
Yes	183 (11.4)	133 (14.5)	50 (7.3)

DMPA, depot medroxyprogesterone acetate; BMI, body mass index; OCP, oral combined contraceptive pill.
Data are n (%), median (1st–3rd quartile), or n.

short-term users showed no reduction in leiomyoma incidence (Appendix 5, available online at http://links.lww.com/AOG/C671).

Results of sensitivity analyses indicated that the potential biases that we evaluated cannot account for our findings (Appendix 6, available online at http://links.lww.com/AOG/C671). In particular, the Cox model assumes that leiomyoma incidence occurs at the end of the interval. Assigning the leiomyoma incidence time to the midpoint of the interval does not

Table 2. Exposure to Depot Medroxyprogesterone Acetate and Leiomyoma Incidence: SELF (Study of Environment, Lifestyle & Fibroids), Detroit, Michigan, 2010–2018 (n=1,232)

DMPA Exposure	Incident Case	Person-Years	Hazard Ratio (95% CI)	
			Minimally Adjusted*	Fully Adjusted†
Never (referent for all)	171	2,779	Ref	Ref
Ever	124	2,544	0.7 (0.6–0.9)	0.9 (0.7–1.2)
Years since last use of DMPA‡				
Within 2	20	660	0.5 (0.3–0.8)	0.6 (0.4–1.0)§
2–3.9	16	317	0.8 (0.5–1.4)	1.0 (0.6–1.8)
4–7.9	27	604	0.8 (0.5–1.1)	0.9 (0.6–1.4)
8 or more	61	963	0.8 (0.6–1.1)	1.1 (0.8–1.5)

DMPA, depot medroxyprogesterone acetate; HR hazard ratio; Ref, referent.
Data are n or hazard ratio (95% CI).
* Cox model with age as the time scale (starting at age of enrollment), with no further adjustment.
† Cox model adjusted for time-varying parity (0, 1–2 births, 3 or more births), time since last birth (within 4 years, 4 or more years, including no births), body mass index (kg/m^2) (lower than 25, 25–29.9, 30–34.9, 35–39.9, 40 or higher), current smoking (yes, no), and household income (less than $20,000, $20,000–50,000, more than $50,000).
‡ Reference is never use.
§ P=.08.

alter the estimate for incidence (aHR 0.6, 95% CI 0.4–1.0). Use of DMPA (and for how long) may be influenced by unmeasured behavioral, clinical, societal, or socio-economic factors. To rule out unmeasured confounding by these factors, we explored the association with temporally remote use of DMPA (8 or more years since last use). These remote users will share many characteristics with other users of DMPA, but they should not have sufficient recent exposure to DMPA to show associations with leiomyoma development. We observed null results for those with 8 or more years since last use of DMPA suggesting that unmeasured factors associated with DMPA use are unlikely to be affecting our findings.

DISCUSSION

In our prospective study of leiomyoma development, we found that use of DMPA within 2 years of an ultrasonographic visit was associated with reduced leiomyoma incidence during the subsequent interval, decreased leiomyoma growth, increased leiomyoma shrinkage, and substantial leiomyoma loss during the subsequent observation interval.

Prior research suggested protective effects of DMPA for leiomyomas but used less convincing study designs than the current prospective study. The Black Women's Health Study found a reduced hazard of incident self-reported leiomyoma diagnoses among current users of DMPA (aHR 0.6, 95% CI 0.4–0.9),[9] and a case-control study in Thailand found reduced prevalence of surgically confirmed leiomyomas among women who had ever used DMPA (odds ratio 0.4, 95% CI 0.4–0.6).[10] Additionally, baseline ultrasonographic data from our SELF study indicated lower leiomyoma prevalence in current DMPA users compared with nonusers.[8] Although existing data on DMPA and leiomyoma growth are limited, in a pilot study of 20 women with clinically diagnosed leiomyomas and menorrhagia from South Africa, monthly treatment with DMPA for 6 months resulted in reduced leiomyoma volume.[21]

The internal consistency of our data on the associations between DMPA exposure and our various measures of leiomyoma development strengthens the plausibility of our findings. The timing of exposure relative to possible effects on leiomyoma development indicated that only the recent exposure (within 2 years) was important for incidence. Given that substantial growth of a lesion is required after initiation for a tumor to reach ultrasonogram-detectable size, the reduction in incidence could be secondary to DMPA effects on growth rather than effects primarily affecting tumor initiation. The extended exposure window we observed for associations with leiomyoma loss (within 4 years of visit), suggests that DMPA can have quite long-lasting biological effects, at least on the small tumors that dominated our sample. A prior study identified changes in blood flow and necrosis in rapidly shrinking leiomyomas.[20] Changes to blood supply or apoptosis pathways during active exposure to DMPA may initiate irreversible cascading events that lead to leiomyoma loss well after DMPA use ends.

At first glance, a protective effect for a progestin is unexpected given the critical roles that progesterone plays in positive leiomyoma growth, including cell proliferation, extracellular matrix formation and suppression of apoptosis (reviewed in Reis[22] and Bulun[23]); however, estradiol is instrumental in the

Table 3. Associations Between Depot Medroxyprogesterone Acetate Exposure and Leiomyoma Growth: SELF (Study of Environment, Lifestyle & Fibroids), Detroit, Michigan, 2010–2018 (n=434)

DMPA Exposure	No. of Growth Intervals	Estimated % Difference in Growth (95% CI)	
		Minimally Adjusted*	Fully Adjusted†
Never (referent for all)	964	Ref	Ref
Ever	395	−11.3 (−19.8 to −1.8)	−10.0 (−18.4 to −0.8)
Years since last use of DMPA‡			
Within 2	75	−45.3 (−54.3 to −34.5)	−42.0 (−51.4 to −30.7)
2–3.9	28	−10.4 (−32.4 to 18.8)	−12.0 (−33.2 to 15.8)
4–7.9	63	4.8 (−14.0 to 27.6)	6.8 (−11.9 to 29.6)
8 or more	229	1.8 (−10.0 to 15.2)	0.6 (−10.7 to 13.3)

DMPA, depot medroxyprogesterone acetate; Ref, referent.
* Minimally adjusted model includes volume of leiomyoma (cm^3) (less than 0.5, 0.5–4.19, 4.2–14.0, greater than 14.1), number of leiomyomas (ordinal 1, 2, 3, 4 or more), and age (continuous).
† Fully adjusted models further adjust for years since last birth (within 5 years, 5 or more years, including no birth), income (less than $20,000, $20–50,000, more than $50,000), employment (employed yes or no), current use of oral contraceptive (yes or no), and age at menarche (ordinal younger than 11, 11, 12, 13, older than 13 years).
‡ Referent is never use.

effect of progesterone through the upregulation of progesterone receptor expression,[24,25] and use of DMPA results in hypoestrogenism.[26] Any resulting reduction in progesterone receptor expression could diminish responsiveness of the tissues to endogenous progesterone as well as the exogenous progestin.

The biological activity of endogenous progesterone and synthetic progestins (reviewed in Hapgood et al[27]) differ in ways that are both progestin and tissue specific. For instance, in lung carcinoma and embryonic kidney cells, medroxyprogesterone acetate has heightened affinity and potency for the glucocorticoid receptor compared with progesterone.[28] Also, in endometrial stromal fibroblasts, treatment with medroxyprogesterone acetate resulted in differential expression of almost 150 genes compared with progesterone.[29] Given these important biological differences, mechanistic studies of myometrial and leiomyoma tissue obtained from women with different exposures to DMPA are needed to investigate the biological pathways at play.

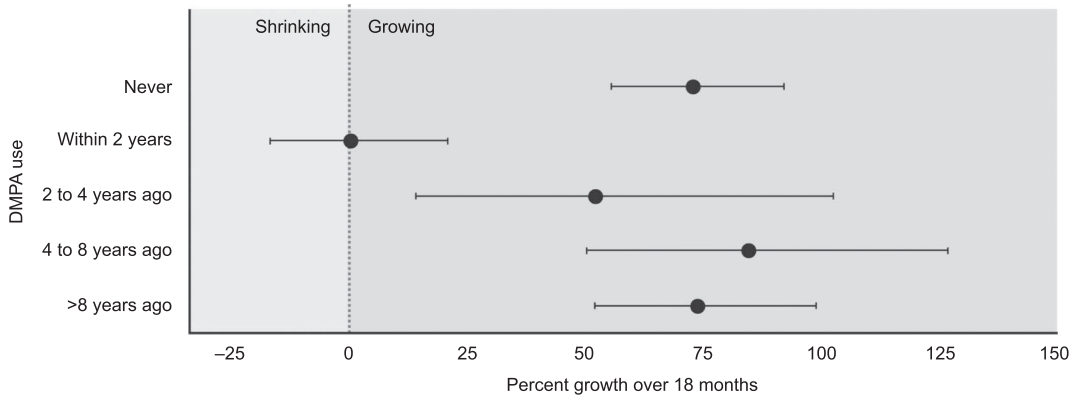

Fig. 2. Estimated growth* per 18 months for depot medroxyprogesterone acetate (DMPA) use (never and categories of years since last use). Estimated percent growth (*solid circle*) and 95% CI (*solid lines*) per 18 months from an adjusted linear mixed model by categories of years since last use of DMPA. Observations from 433 participants (1,351 pairs of matched leiomyomas). Exposure to DMPA within 2 years results in no growth. Never exposure to DMPA or exposure to DMPA more than 2 years ago results in strong positive growth (an average 52–85% increase in volume per 18 months). *Estimated with covariate values based on the categories with the highest sample frequencies: volume of leiomyoma at start of interval 0.5 to less than 4.2 cm^3, 32 years old, two leiomyomas, employed, income less than $20,000, no birth within 5 years, age 12 years at menarche, no use of oral contraceptive at visit. For ease of interpretation, the estimated mean change in volume per 18 months (μ) from the fitted model was transformed to percent growth per 18 months ($\exp(\mu)-1)*100$ (Appendix 1, available online at http://links.lww.com/AOG/C671).

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Table 4. Associations Between Depot Medroxyprogesterone Acetate Exposure and Leiomyoma Loss: SELF (Study of Environment, Lifestyle & Fibroids), Detroit, Michigan, 2010–2018 (n=539)

DMPA Exposure	No. Loss/No. Exposed (%)*	Risk Ratio (95% CI)	
		Minimally Adjusted†	Fully Adjusted‡
Never (referent for all)	143/663 (21.6)	Ref	Ref
Ever	105/358 (29.3)	1.3 (1.1–1.7)	1.3 (1.0–1.6)§
Years since last use of DMPA‖			
Within 2	32/83 (38.6)	1.8 (1.3–2.4)	1.6 (1.1–2.2)
2–3.9	16/32 (50.0)	2.3 (1.6–3.4)	2.1 (1.4–3.1)
4–7.9	17/60 (28.3)	1.2 (0.8–1.9)	1.2 (0.8–1.9)
8 or more	39/182 (21.4)	1.0 (0.7–1.3)	0.9 (0.7–1.3)

DMPA, depot medroxyprogesterone acetate.
* Count of women with a reduced number of leiomyomas in a successive visit/number of follow-up visits.
† Minimally adjusted model is adjusted for number of leiomyomas (ordinal 1, 2, 3 or more), largest leiomyoma volume (cm^3) (less than 0.5, 0.5 to less than 4.2, 4.2–33.5, greater than 33.5), age at visit (continuous), and months between visits (continuous).
‡ Fully adjusted models further adjust for years since last birth (within 4 years, 4 or more years, including no birth), BMI (kg/m^2) (lower than 25, 25–29.9, 30–34.9, 35–39.9, 40 or higher), and education (high school or less, more than high school).
§ $P=.049$.
‖ Referent is never use.

Our study has limitations. First, we lack accurate data on duration of the last episode of DMPA use. However, we have reasonably good data on time since last DMPA use. Recall accuracy of hormonal contraceptive use has been reported to be high, and we collected these data using a detailed telephone interview, which enhances data quality.[30] Measurement error in the time since last DMPA use is unavoidable because we collected age at last use instead of date at last use. Nevertheless, the exposure showing strong associations with leiomyoma development was recent use, which is likely to be well-remembered. Further study with prospective follow-up of first-time DMPA users who will continue to use for variable periods of time would be valuable for evaluating the importance of length of DMPA use. Secondly, as with other studies of leiomyoma growth, our analyses rely on leiomyomas that could be tracked over time; lost leiomyomas are not included, which results in an overestimation of positive growth. Nevertheless, we were able to expand the growth findings in a clinically meaningful way by analyzing leiomyoma loss as a separate outcome. Thirdly, ultrasonography introduces measurement error that is greater for smaller leiomyomas.[13] We address this limitation by accounting for differences in measurement error by leiomyoma size in our model (Appendix 1, http://links.lww.com/AOG/C671).

Our study's unique strengths include a large community sample with prospective ultrasonographic screening and examination of multiple aspects of leiomyoma development. Additionally, a focus on Black women allowed us to generate estimates relevant to the group experiencing the greater burden of this health condition. Finally, multiple sensitivity analyses indicated that our results are robust to alterations in model specification and assumptions. Importantly, unmeasured differences between women who use and those who do not use DMPA cannot explain our results. Given the prospective study design among women with no previous diagnosis of leiomyomas, our results for leiomyoma incidence should be widely generalizable. However, examination of leiomyoma growth in a sample with more large leiomyomas is needed to assess generalizability of our leiomyoma growth results.

Depot medroxyprogesterone acetate was approved for contraception by the U.S. Food and Drug Administration in 1992; thus, it was available as our study cohort came of age. Depot medroxyprogesterone acetate is currently used by 2% of women in the United States[31] and is more commonly used by African American women (12% of those using any form of contraceptive[32]). In other parts of the world, usage can range as high as 23%.[33] A highly effective form of contraception, DMPA does have adverse effects that can result in high discontinuation rates,[34] and the U.S. Food and Drug Administration (but not the American College of Obstetricians and Gynecologists) has recommended that continuous use not exceed 2 years to limit possible bone loss.[35] Our findings point to potential noncontraceptive benefits of DMPA. Nevertheless, use of DMPA as a treatment to optimally prevent leiomyomas or delay symptoms will need further study. Individual choice of type of contraception must

always balance multiple personal and medical risks and benefits.

In conclusion, we find that use of DMPA is associated with reduction in leiomyoma incidence and growth, with concomitant leiomyoma shrinkage and loss. Use of DMPA may limit early leiomyoma development, which could delay symptom progression and reduce the need for invasive treatment.

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