

The Impact of Progestin-only Contraception on Adolescents with Macromastia

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Background: Progestin-only contraception has become increasingly popular among adolescents. However, patients, parents, and providers share concerns regarding the potential impact that progestin-only contraception may have on breast growth. We sought to explore the impact of progestin-only contraception on breast hypertrophy and symptomatology in adolescents with macromastia.

Methods: Patients between the ages of 12 and 21 years undergoing reduction mammoplasty were prospectively assessed for baseline and postoperative breast symptomatology and medication use. The medical records of female controls within the same age range were retrospectively reviewed.

Results: A total of 378 participants with macromastia and 378 controls were included in analyses. A higher proportion of controls used progestin-only methods compared with participants with macromastia (28.0% versus 5.3%, $P < 0.001$). The most commonly prescribed methods were the depot medroxyprogesterone acetate injection (31.0%), levonorgestrel-containing intrauterine device (31.0%), and subdermal implant (26.2%). Patients with macromastia who used progestin-only contraception had a greater amount of breast tissue resected during reduction mammoplasty ($P = 0.04$), reported greater musculoskeletal pain ($P = 0.008$), and were roughly 500% more likely to experience breast pain (odds ratio, 4.94; 95% confidence interval, 1.58–15.47; $P = 0.005$) than those with macromastia who never used hormonal contraception.

Conclusions: Adolescents with macromastia who use progestin-only contraception may have greater breast hypertrophy and worse breast and musculoskeletal pain. When appropriate, providers may wish to consider other contraception methods for patients who are at-risk for breast hypertrophy or those who suffer from macromastia-related symptoms. (*Plast Reconstr Surg Glob Open* 2021;9:e3421; doi: [10.1097/GOX.0000000000003421](https://doi.org/10.1097/GOX.0000000000003421); Published online 12 February 2021.)

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INTRODUCTION

In the United States, hormonal contraceptives (HCs) are one of the most widely prescribed medications for young women.¹ In addition to preventing unintended pregnancy, HCs are used by roughly one-third of American young women to manage a host of endocrine and gynecologic conditions.^{2,3} Despite their contraceptive and medical benefits, HCs are not without adverse effects. Most notably, the combination oral contraceptive pill (COC), containing both estrogen and progestin, may increase a woman's risk of thromboembolic disease, cerebrovascular and cardiovascular event, and potentially, breast cancer.⁴⁻⁶ High-dose COCs have also been associated with migraine, hyperlipidemia, and breast-swelling and tenderness.^{7,8} To mitigate these estrogen-mediated effects, COCs available today contain considerably lower ethinyl estradiol doses than first-generation

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formulations. However, low-dose COCs may have diminished contraceptive efficacy in overweight and obese women.⁸

As a result, progestin-only contraception has become an attractive alternative. Lacking ethinyl estradiol, many progestin-only formulations do not carry the same risk profile as COCs, and their efficacy is not impacted by body mass index (BMI).^{9,10} These options include depot medroxyprogesterone acetate (DMPA) injections and long-acting reversible contraception (LARC) methods such as the levonorgestrel-containing intrauterine device and subdermal implant. LARC has gained considerable popularity among sexually active adolescents, who may struggle with daily pill adherence and proper barrier method use.^{11,12}

With the rising number of adolescents presenting with symptomatic macromastia,¹³ many patients and parents are increasingly concerned that exposure to the exogenous hormones found in HCs may exacerbate breast size and symptoms. Although there is a dearth of peer-reviewed articles exploring this association, a simple internet search yields countless lay articles suggesting a causative relationship.^{14,15} To address this gap in the current literature, we explored the association between progestin-only contraception and macromastia using a retrospective, case-control study design and standardized clinical assessment.

METHODS

Macromastia Cohort

After obtaining approval from Boston Children's Hospital Committee on Clinical Investigation (Protocol number: X08-10-0492), patients with macromastia were enrolled during their initial consultation at the Boston Children's Hospital Adolescent Breast Center from 2007 through 2018. Written informed consent was obtained from these participants, and a parent/guardian if under 18 years. Eligible participants were nulliparous and 12 to 21 years old at baseline. A diagnosis of macromastia was made using symptomatology, physical examination, and modified Schnur criteria.^{16,17} The Schnur criteria are a sliding scale that uses patient's height, weight, and anticipated amount of breast tissue resected to determine if the motivation for reduction mammoplasty is primarily medical or cosmetic.^{16,17} Aside from rare cases in which the patient is extremely symptomatic, stable weight and breast size for 1 year are required before proceeding with reduction mammoplasty.

Defining Macromastia Severity

Macromastia severity was measured using the normalized amount of tissue resected, and degree of clinical impairment. Each patient's body surface area (in square meters) was calculated using their height and weight measurements according to the DuBois and DuBois formula.^{18,19} To normalize the total amount of breast tissue resected during reduction mammoplasty across a variety of body sizes, the amount of tissue resected for each patient was divided by their body surface area.

Clinical impairment was assessed at baseline. Patients were asked to separately rate the severity of their typical (1) neck, (2) shoulder, and (3) back pain using a continuous

pain scale ranging from 0 (no pain) to 10 (worst pain). A musculoskeletal pain score was then calculated by summing each of these 3 pain scores, such that values ranged from 0 (no pain) to 30 (worst pain). Patients were also asked to indicate if they had breast pain, inframammary fold intertrigo, and difficulty finding properly fitting clothing or exercising due to their breast size.

After the first postoperative year, breast regrowth was assessed using physical examination, visually using 2-dimensional photographs, and bra fitting. Breast measurements may also be taken by clinical staff and can include sternal notch to nipple distance, and thoracic circumference at the most prominent point and at the inframammary fold. Postoperative breast growth was considered glandular when BMI remained stable in the presence of a clinical assessment consistent with breast gland hypertrophy. All other instances of regrowth were attributed to weight gain.

Control Cohort

The Boston Children's Hospital Committee on Clinical Investigation granted a waiver of written consent to retrospectively review the medical records of female controls consecutively seen in 2018 by the Division of Adolescent/Young Adult Medicine at the same institution for routine healthcare maintenance visits. Controls were of the same age as those of the breast cohort, and eligible candidates had complete medical records with no current or prior breast condition or breast surgery. A 1:1 ratio of controls to participants with macromastia was ensured for analyses.

Clinical staff collected all subjects' height and weight during their initial consultation or routine well visit. BMI category was determined using either the Centers for Disease Control and Prevention's Child and Teen BMI percentile calculator²⁰ or Adult BMI calculator.²¹ All previous HC use was recorded for controls. For macromastia patients, any HC used up to 3 months before reduction mammoplasty was used for analyses, except where explicitly indicated.

Data Management and Statistical Methods

Data were collected using REDCap (Research Electronic Data Capture).²² Statistical analyses were conducted using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Independent 2-sample *t* tests, independent-samples Mann-Whitney U tests, Pearson χ^2 , and Fisher exact tests were used to compare demographics and clinical information between groups when appropriate. As previous studies have found an association between DMPA injection and weight gain,^{23,24} macromastia group sub-analyses were conducted to compare the clinical information of DMPA users with those who used other progestin-only methods. A missing data threshold of 20% was used for analyses. A two-sided *P* < 0.05 was considered statistically significant for all analyses.

RESULTS

A total of 378 participants with macromastia and 378 controls were included in analyses. Both the macromastia and control cohorts were of similar mean age at menarche

(11.9 ± 1.5 years versus 11.8 ± 1.3 years, $P = 0.28$) and baseline evaluation (18.1 ± 1.7 years versus 18.3 ± 2.1 years, $P = 0.10$). The macromastia cohort had a significantly higher median BMI (27.2 kg/m² versus 24.3 kg/m²) and BMI percentile (91st versus 78th) compared with controls ($P < 0.001$). Additionally, a greater proportion of macromastia patients (250, 66.1%) were classified as overweight or obese compared with controls (172, 45.5%; $P < 0.001$).

A higher proportion of controls used HCs of any method (64.8% versus 37.8%; $P < 0.001$), and specifically progesterin-only contraception compared with the macromastia cohort (28.0% versus 5.3%; $P < 0.001$; Table 1). Within the entire sample, the most commonly used progesterin-only methods were the DMPA injection and levonorgestrel-containing intrauterine device (31.0%, each), followed by the subdermal implant (26.2%) and progesterin-only pill (11.9%). The distribution of progesterin-only methods used did not vary between cohorts ($P = 0.09$).

Within both cohorts, the proportion of overweight or obese participants did not vary between progesterin-only users and those who had never used an HC ($P > 0.05$, both). Additionally, the proportion of overweight and obese DMPA users did not differ from that of other progesterin-only methods for each cohort ($P > 0.05$, both).

Breast Hypertrophy and Symptomatology

Participants with macromastia who had ever used a progesterin-only method had a larger median normalized amount of breast tissue resected during reduction mammoplasty than their HC-naive counterparts (959.9 g/m² versus 735.9 g/m²; $P = 0.04$; Table 2). DMPA users and

those who used other progesterin-only methods had a comparable normalized amount of breast tissue removed ($P = 0.74$).

Most macromastia participants who had used a progesterin-only method were using one at the time of their baseline evaluation (19/20, 95.0%). These baseline users had a higher mean total musculoskeletal pain score (22.8 versus 18.3; $P = 0.008$) and were roughly 500% more likely to report having breast pain than their HC-naive counterparts [odds ratio, 4.94; 95% confidence interval (CI), 1.58–15.47; $P = 0.005$]. The incidence of inframammary intertrigo, and difficulty finding clothing that fit and exercising due to breast size did not vary between the progesterin-only and HC-naive groups, or between DMPA users and those using other progesterin-only methods ($P > 0.05$, all).

Postoperative Breast Growth

The majority of the macromastia cohort (368, 97.4%) was at least 1 year out from surgery and was assessed for postoperative breast growth, with a median follow-up time of 2.2 years (minimum, 1.0; maximum, 10.4; interquartile range, 3.7). Roughly 5% ($N = 20$) of patients with a follow-up assessment experienced postoperative breast regrowth, with a little over half of all instances due to glandular proliferation (11, 55.0%) as opposed to weight gain (9, 45.0%). All patients with regrowth, except for one, had a stable weight and breast size before surgery. This sole patient was HC-naive and experienced rapid, symptomatic breast growth that necessitated surgery before breast size could stabilize.

Table 1. Hormonal Contraception Use by Cohort

	Macromastia (N = 378)	Control (N = 378)	P
Hormonal contraception use, N (%)	143 (37.8)	245 (64.8)	<0.001
Combined estrogen and progesterin methods	123 (32.5)	139 (36.8)	<0.001
Progesterin-only methods	20 (5.3)	106 (28.0)	
None	235 (62.2)	133 (35.2)	
Progesterin-only contraception methods, N (%)	N = 20	N = 106	0.09
Depot medroxyprogesterone acetate	10 (50.0)	29 (27.4)	
Subdermal implant	6 (30.0)	27 (25.5)	
Progesterin-only pill	2 (10.0)	13 (12.3)	
Levonorgestrel-containing intrauterine device	2 (10.0)	37 (34.9)	

Table 2. Macromastia-related Symptomatology by Hormonal Contraception Use

	Macromastia Progesterin-only Users	Macromastia HC* Non-users	P
Breast hypertrophy	N = 118	N = 235	—
Median (IQR) normalized breast tissue resected, g/m ²	959.9 (794.8)	735.9 (339.8)	0.04
Clinical impairment	N = 19†	N = 235	—
Mean ± SD musculoskeletal pain score	22.8 ± 5.7	18.3 ± 7.1	0.008
Breast pain, N (%)	14 (77.8)	95 (41.5)	0.005
			4.94 (1.58–15.47)‡
Inframammary intertrigo, N (%)	8 (41.1)	98 (42.2)	0.86
Difficulty finding clothing that fit due to breasts, N (%)	17 (89.5)	216 (93.5)	1.09 (0.42–2.87)‡
Difficulty exercising due to breasts, N (%)	15 (78.9)	198 (85.7)	0.88
			1.18 (0.15–9.48)‡
			>0.99
			0.83 (0.23–3.04)‡

*Hormonal contraception.

†Inclusive of patients using progesterin-only contraception at the time of baseline evaluation.

‡Odds ratio (95% CI).

Fewer than one-tenth (23/368, 6.3%) of all patients assessed for postoperative growth used progestin-only contraception during the postoperative period. Postoperative progestin-only contraception use did not increase the likelihood of experiencing postoperative breast growth (OR, 2.35; 95% CI, 0.62–8.96; $P = 0.19$) or regrowth specifically due to glandular proliferation (OR, 3.35; 95% CI, 0.64–17.65; $P = 0.17$) or weight gain (OR, 1.36; 95% CI, 0.16–11.6; $P = 0.56$). The incidence of any postoperative breast growth, or regrowth due to glandular proliferation or weight gain among DMPA users did not differ from those using other progestin-only methods ($P > 0.05$, all).

DISCUSSION

Progestin-only contraception continues to grow in popularity among young women as an attractive alternative to estrogen-containing methods.¹² Unlike ethinyl estradiol, the contraceptive efficacy of progestin does not diminish at higher BMIs and largely does not carry the same risk profile.^{9,10} The majority of progestin-only methods fall under the umbrella of LARC, which removes user error and has lower failure rates.^{11,12} LARC has been shown to significantly reduce unintended pregnancies among teenagers, who generally have poorer daily pill compliance and greater barrier method user error than adults.^{11,12}

There are countless lay articles across the internet that suggest HCs may cause breast hypertrophy.^{14,15} As such, many young patients with macromastia and their parents worry that progestin-only contraception may exacerbate breast hypertrophy and symptomatology. This study aimed to address this concern by exploring the impact of progestin-only contraception on breast-related symptomatology in adolescents with macromastia.

Controls in our sample were more likely to use progestin-only HC methods, particularly LARC, whereas patients with macromastia were more likely to use COCs. The usage of progestin-only methods among our controls is considerably higher than that reported in the current literature.¹² Our relatively high incidence of progestin-only contraception use may be amplified as our control cohort was recruited from our institution's Division of Adolescent/Young Adult Medicine, which has a specialty clinic for LARC.

Impact of Progestin-only Contraception on Breast Hypertrophy and Symptomatology

Participants with macromastia who used progestin-only contraception had a greater degree of breast hypertrophy as measured by the normalized amount of tissue resected during reduction mammoplasty, more severe musculoskeletal pain, and were roughly 500% more likely to have breast pain than their HC-naïve counterparts. Previous studies have found that DMPA injection is associated with a weight gain of <3 kg.^{23,24} Weight gain following progestin-only initiation, particularly among DMPA users, may be responsible for the more severe breast hypertrophy and related breast and musculoskeletal pain observed in our macromastia cohort. However, it is unlikely that weight gain alone accounts for this discrepancy, as both

progestin-only contraception use and, specifically, DMPA use were not associated with being overweight or obese.

Growing evidence suggests that exogenous progestin may have a mitogenic effect on breast tissue.²⁵ Although patients with macromastia who used progestin-only contraception had greater breast hypertrophy, use of progestin-only methods following reduction mammoplasty was not associated with breast regrowth. These findings suggest that progestin-only contraception may stimulate and even exacerbate initial breast gland proliferation, but may not be associated with continued glandular proliferation. More research is needed concerning the effects of exogenous progestin on the developing breast and breast gland proliferation.

Several factors must be considered when prescribing progestin-only contraception. Progestin-only methods have an androgenic effect and may result in worsened acne, oily skin, hirsutism, and potentially android obesity and androgenic alopecia.^{26,27} For this reason, prescribers may wish to avoid progestin-only contraception in patients with hormonal acne, polycystic ovary syndrome, or other endocrine dysregulation. With prolonged use, progestin-only methods typically result in decreased menstrual bleeding and even secondary amenorrhea.²⁸ Although many patients choose progestin-only contraception for this reason, this may cause considerable anxiety in sexually active patients. If this side effect is worrisome, patients can be advised to use home pregnancy tests on a monthly basis. The progestin-only pill may not be suitable for sexually active patients who struggle with daily pill adherence. Unlike the COC, the progestin-only pill requires the use of a backup contraceptive method if the patient misses a single dose.²⁹ For these patients, providers should instead consider LARC methods (such as the levonorgestrel-containing intrauterine device) and subdermal implant.

Although uncommon in adolescents, DMPA injection may be associated with an increased risk of thromboembolic disease or breast cancer.^{9,30,31} Additionally, it is well-established that DMPA can exacerbate bone mineral density loss and lead to osteoporosis.³² Cromer et al found that adolescents using DMPA lost an annual 1.4% spine and 2.2% femoral neck bone density per year, whereas non-users gained 3.8% and 2.3% bone density, in these respective locations.³² Individual risk factors and family history must be taken into consideration before prescribing DMPA injections, and monitoring of bone health should be considered.

Limitations must be acknowledged. Unlike the control cohort who were generally followed by our institution for the entirety of their adolescence, the macromastia cohort largely received their primary care elsewhere. As a result, their medication history was self-reported and subject to recall inaccuracies, and duration of contraceptive use was often unable to be determined. Additionally, women often use multiple HC formulations over the course of adolescence. Due to the nature of this study, we were unable to measure the impact of switch-use on breast hypertrophy and symptomatology. As the number of progestin-only users was relatively low, analyses may be underpowered. We recognize that the amount of tissue resected is only an approximation for macromastia severity. To minimize variability, all patients underwent the same surgical technique by the

same surgeon. Although the goal of surgery is to remove only the amount of tissue necessary so that the breasts are in proportion with the patient's overall frame, this amount may also be dictated by the patient's individual preferences.

Given prescribing patterns within the United States continue to shift in favor of progestin-only methods,¹² and that controls were captured over the course of a single year (2018), we recognize that case-control analyses may reflect potential sampling bias. To assess for bias, we compared HC and progestin-only use among controls and patients with macromastia who were recruited during the last 3 years of the study. In these sub-analyses, overall HC and progestin-only contraception use continued to be significantly greater among controls ($P < 0.001$, both).

CONCLUSIONS

Our findings suggest that although use of progestin-only contraception is not associated with postoperative breast regrowth in young women with macromastia, it may be associated with greater baseline breast hypertrophy and worsened breast and musculoskeletal pain. When appropriate, providers may wish to consider other methods of contraception for patients who are at-risk for breast hypertrophy or those who are symptomatic.

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