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Birth control medications decrease asthma incidence

Dawn C. Newcomb, PhD

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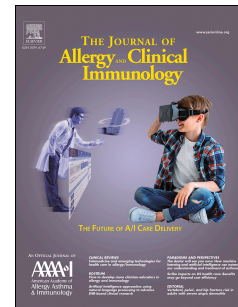
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1 Birth control medications decrease asthma incidence

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3 Dawn C. Newcomb, PhD

4 Department of Medicine and Department of Pathology, Microbiology, and Immunology

5 Vanderbilt University Medical Center

6 Nashville, TN 37232

7 Dawn.newcomb@vumc.org

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There is a sex difference in asthma incidence and prevalence that changes at puberty. As children, boys have a higher prevalence and incidence of asthma compared to girls, but as adults, women have a higher prevalence and incidence of asthma compared to men.¹ Further, sex hormones regulate asthma pathogenesis. Women with asthma report fluctuations in asthma symptoms and exacerbations during menses, pregnancy, and menopause, suggesting a role for ovarian hormones.^{2,3} Androgens, including dehydroepiandrosterone (DHEA), increase in males compared to females during puberty, and increases in DHEA in males is associated with increases in lung function, decreases in asthma symptom scores, and decreases in asthma prevalence.⁴ Androgens also decrease type 2 and IL-17A-mediated airway inflammation in mouse models of asthma, while ovarian hormones, including estrogen and progesterone, increase type 2 and IL-17A-mediated airway inflammation (reviewed in 5). Though it is recognized that sex hormones regulate asthma incidence and pathogenesis, it is not well understood how hormonal contraceptives influence asthma incidence, prevalence, control of asthma symptoms, and asthma exacerbations in women of reproductive age. Approximately 25.8% of reproductively aged women in developed countries use hormonal contraceptives.⁶ Therefore, understanding the impact of hormonal contraceptive use on asthma onset and asthma symptoms is critical for treating women with asthma.

In this current issue of the *Journal*, Nwaru et al show that hormonal contraceptives reduce the incidence of asthma in women, and a longer duration of hormonal contraceptive use further reduced the incidence of asthma (summarized in Figure 1).⁷

Studying how hormonal contraceptives alter asthma incidence of symptoms is difficult due to the many types and dosages of hormonal contraceptives and different phenotypes of asthma. In 2018, this same group published a meta-analysis containing studies that had reported both increased and decreased risks of current asthma with oral hormonal contraceptive use.⁸ Small sample sizes, potential selection bias in cohorts, and limitations in the collections of asthma incidence and asthma control made it difficult to determine if hormonal contraceptives altered asthma incidence or asthma control in women. In this current study, Nwaru and colleagues use an open, retrospective cohort established from the Optimum Patient Care Research Database (OPCRD), a database comprised of 630 primary care practices in the United Kingdom and over 6 million patients to study hormonal contraceptive use and asthma incidence. Women, ages 16 to 45 years, were included in the analysis and variables were extracted using an exhaustive list of electronic health record read codes to determine onset of asthma, hormonal contraceptive use, pregnancy, smoking, body mass index, gynecological conditions, and other confounding variables. Using these inclusion/exclusion criteria, 564,896 women were included from the OPCRD in this extensive study. Electronic health records from women were tracked over a 17-year period, starting from study baseline (January 1, 2000), date of registration with provider, or when turning 16 years old. Years that women were pregnant were excluded in the analysis, and women exited from the study with the first record of an asthma event, deregistration from a practice, turning 45 years old, death, or end of study follow-up (December 16, 2016). Cofactors such as obesity and smoking status are linked to an increased risk of asthma, and the large cohort size allowed the authors to determine if

there was an interaction between obesity and/or smoking status and hormonal contraceptive use in asthma.⁹ No interaction between BMI and hormonal contraceptive use was found, but a significant interaction between hormonal contraceptive use and smoking was determined. The risk of developing asthma was lower in women that smoked on hormonal contraceptives than in non-smokers. This is an interesting finding that warrants further study.

Importantly, having a cohort of over a half a million women allowed the authors to group hormonal contraceptives into categories of estrogen and progesterone combination therapies or progesterone-only therapies. With so many different types and dosages of birth control medications, classifying these medications into two categories provided the first insight on how use of estrogen and progesterone combination or progesterone only therapies reduced the risk of new-onset asthma. These findings were extended to determine that longer duration of hormonal contraceptives use was also associated with lower risk of asthma onset compared to non-use. Determining if different routes of hormonal contraceptive administration (e.g. oral, intrauterine, transdermal, etc.) altered the hazard ratios for asthma incidence would have been useful, but the authors note that this information was not consistently recorded in the database and these analyses were not possible. While this article convincingly shows that hormonal contraceptives decrease asthma incidence and this is associated with longevity of use, it does not show data on how hormonal contraceptives use affects FEV1, asthma symptom scores, health care utilization, or asthma exacerbations. In the discussion section,⁷ the authors state these analyses will be presented in subsequent articles. These findings will be

critical for determining how hormonal contraceptives affect asthma symptoms and exacerbations in women currently with asthma.

Defining the associations between hormonal contraceptive use (and duration of treatment) and asthma incidence is imperative in determining how reducing sex hormone fluctuations alter asthma onset and potentially asthma pathogenesis. Additional studies are needed to elucidate how use of exogenous sex hormones during menopause or how changes in sex hormone levels during pregnancy affect asthma incidence as well as asthma control and exacerbations in women that currently have asthma. Defining these changes in women will provide the foundation necessary for designing mechanistic studies that determine how hormonal contraceptives and/or fluctuations in ovarian hormones during different reproductive phases of life alter pathways important in driving the hallmarks of asthma - airway inflammation, smooth muscle constriction, and/or mucus production.

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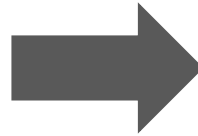
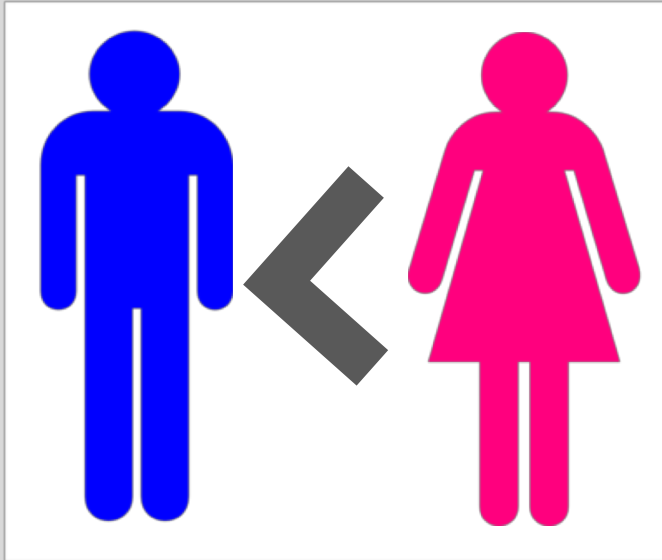
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Figure 1. Hormonal contraceptive use decreases asthma onset. Left panel: schematic showing sex difference in asthma as adults with women having increased asthma incidence and prevalence compared to men. Right panel: Hormonal contraceptive use decreasing asthma incidence in women of reproductive age. Longer duration of hormonal contraceptive use further reduces risk of asthma onset.

Asthma incidence
in adulthood



Women
(17-45 years old)

