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## **Do you inquire about hormonal treatment in female patients consulting for new onset asthma or asthma exacerbation?**

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In this issue of the journal, Hansen and co-authors [1] present the findings of a new study investigating the incidence of asthma in women after initiation of hormonal contraceptive treatment (HC), as compared to women who had never used HC. They used Danish national registers to (i) identify 30,669 women who initiated HC treatment between 2008 and 2017 and had never had asthma at time of HC initiation; (ii) match these women with 5 non-asthmatic women of the same age who had never used HC; and (iii) assess new onset asthma (defined as two redeemed prescriptions of inhaled corticosteroids within two years) over the years of HC use, as compared to non-users. The mean follow-up was 2.1 years. They showed a higher incidence of asthma in HC users, particularly among women who started HC before the age of 18 years. The hazard ratio for asthma incidence in women who started HC between 14-17 years, as compared to non-users was 1.71 (95%CI 1.50 to 1.95). Both second and third generation combined (estrogen + progestin) oral pills, and also progestin-only oral pills were significantly associated with a higher risk of developing asthma.

There have been very few longitudinal studies investigating the association between HC and asthma onset and these studies have provided inconsistent findings, some studies reporting an increased risk of asthma in women using HC whereas others highlight a decreased risk. The effect of HC treatment, similarly to the effect of hormonal treatment for menopause, is particularly difficult to appraise in observational studies, and findings might be heavily biased. An “indication bias” might occur if those women prescribed with HC at an early age, or conversely the small group of women never prescribed with HC, are different from other women with regards to their health condition. In addition, a “selection” bias might occur, particularly in cross-sectional studies or when HC use is assessed at inclusion. For example, it might be that before the study, some women had started HC but discontinued HC use because they had a concomitant asthma exacerbation. In this case, at the study

inclusion, asthmatic women would be less likely to use HC or may have a shorter duration of HC use, which might suggest a false “protective” effect. The reverse selection bias might also occur if there was associated symptom relief. In prospective studies of adult women, women with pre-existing asthma are excluded, and hence, it might be that the women with the greatest risk of developing asthma after HC initiation, are not included in the analysis. Despite careful investigation, such biases are often difficult to appraise. Compared with previous studies, one of the major strengths of the study by Hansen et al. relies on its longitudinal design, and more specifically, the investigation of asthma onset in all women who started using HC. It therefore adds new important information, as it is the first large study investigating the risk of asthma onset after HC initiation.

In the study by Hansen et al., the use of register-based data allowed inclusion of a large number of women and to investigate various subtypes of HC, which is another strength of the study. However, the register-based design does not permit accounting for important individual covariates. Models were adjusted for income and urbanization, but the authors could not adjust for age at menarche or overweight/obesity. If women initiating HC before the age of 18 years comprise more girls with early menarche, this might have confounded the results, as an earlier age at puberty increases the risk of asthma [2]. Overweight and obesity are also important risk factors for asthma, and studies have highlighted strong interplays between sex hormones, adiposity and the metabolic status and asthma. Again, the literature with regards to HC is inconsistent. In the fifth decade follow-up of the Tasmanian Longitudinal Health Study, increasing years of pill use after menarche was associated with an increased risk of current asthma at age 44 years in overweight/obese women but with a reduced risk of asthma in normal-weight women [3]. In contrast, in a recent analysis of a large primary care database of 16- to 45-year-old women in the UK, longer duration of HC use was associated with a lower risk of new-onset asthma, and BMI did not modify this association [4].

Although no information on obesity was available in the study by Hansen et al., the authors advocate that obesity or weight gain might be considered as an intermediate factor (HC affecting weight gain which in turn affects asthma development). With this causal pathway in mind, it is correct not to adjust for obesity. However, one cannot conclude from the study findings, if the higher risk of asthma in HC users might be due to an indirect effect of HC through an increase in body weight, a more “direct” effect of exogenous female sex hormones, or residual confounding (e.g. if for any reason girls starting pill before the age of 18 are different to other girls with regards to asthma risk factors, including age at menarche, obesity, physical activity, diet, socio-economic status, or early-life exposures). Further studies with mediation analysis could be useful.

While the direct effect of female sex hormones in asthma remains inconclusive, the study by Hansen et al. [1] nevertheless suggests that young women starting hormonal contraceptives are at increased risk of developing new asthma within the few years after HC initiation. Whatever the underlying mechanisms, this finding is to be accounted for in clinical practice.

Of note, the study by Hansen et al. does not address the question of asthma progression in an asthmatic woman who starts using HC. The findings of this study therefore cannot help answer the question addressed to GPs, allergists or pulmonologists of whether it is safe to initiate hormonal treatment in women with asthma. In a recent analysis of women with asthma in the Optimum Patient Care Research in the UK, use of combined HC was associated with a reduced risk of severe asthma exacerbation compared with non-use [5]. It has been suggested that hormonal treatment might be particularly useful in patients with premenstrual asthma [6], possibly through reducing hormonal fluctuations across the cycles. However, a small RTC has failed to show supportive evidence [7] and further studies are required.

Conversely, the findings of the study by Hansen et al. do stress the need for inquiring about hormonal treatment initiation in teen girls or young women presenting for new asthma onset. To date, hormonal contraception, and more generally hormonal treatments, have received little attention in current guidelines and are not included in the lists of possible asthma triggers that should be screened when assessing asthma. From a public-health perspective; it is known that women are at higher risk of asthma than men after puberty, although reasons for this are still unclear [8]. If the association highlighted in the paper by Hansen et al. is causal, given the huge proportion of women using HC, then the part of adult-onset asthma in women attributable to HC use might be substantial. Further studies are required to investigate this hypothesis, assess the part mediated by weight change in women using HC, whether HC use is associated with asthma incidence if weight increase is controlled, and then, whether hormonal treatment discontinuation might resolve asthma in these women.

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