Maternal asthma severity and control during pregnancy and risk of offspring asthma

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Background: Severe and uncontrolled asthma during pregnancy has been linked to several unfavorable perinatal outcomes. However, current knowledge on the association between the severity and control of maternal asthma and offspring asthma is sparse.

Objective: We sought to investigate the extent to which offspring asthma is influenced by maternal asthma severity and control during pregnancy.

Methods: We performed a prospective population-based cohort study. Using linkage of Danish national registers, we constructed a cohort of 675,379 singletons, of which 15,014 children were born to asthmatic mothers. Among them, 7,188 children were born to mothers with active asthma during pregnancy. We categorized mothers with active asthma into 4 groups based on dispensed antiasthma prescriptions and on use of medical services: mild controlled, mild uncontrolled, moderate-to-severe controlled, and moderate-to-severe uncontrolled asthma. The outcomes were offspring early-onset transient, early-onset persistent, and late-onset asthma. We estimated prevalence ratios (PRs) of each phenotype of asthma using a log-binomial model with 95% CIs.

Results: Higher prevalence of early-onset persistent asthma was observed among children of asthmatic mothers with mild uncontrolled (PR, 1.19; 95% CI, 1.05-1.35), moderate-to-severe controlled (PR, 1.33; 95% CI, 1.09-1.63), and moderate-to-severe uncontrolled asthma (PR, 1.37; 95% CI, 1.17-1.61) compared with those of mothers with mild controlled asthma. A borderline increased prevalence of early-onset transient asthma was observed among children of mothers with uncontrolled asthma.

Conclusion: Maternal uncontrolled asthma increases the risk of early-onset persistent and transient asthma. If replicated, this could suggest that maintaining asthma control in pregnancy is an area for possible prevention of specific phenotypes of offspring asthma. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Asthma, cohort study, control, early onset, late onset, phenotype, pregnancy, severity*

Asthma is the most common chronic disease complicating pregnancy, affecting 3% to 9% of all pregnancies.[1-3] International guidelines recommend that asthma during pregnancy should be managed in the same manner as for nonpregnant women to maintain asthma control.[4] Nevertheless, a survey revealed that approximately 29% of asthmatic women would discontinue asthma medication during pregnancy, mainly for fear of adverse effects on the fetus,[5] despite accumulating evidence on the safety of inhaled corticosteroid and β_2-agonist use during pregnancy.[4,6] Correspondingly, about one third of the women experienced uncontrolled asthma during pregnancy.[7]

Poorly controlled asthma during pregnancy can deprive the fetus of oxygen and thus affects fetal development negatively.[8] Studies have linked uncontrolled asthma to preterm birth, low birth weight, and fetal growth restriction,[9-11] which are known risk factors for asthma.[12] Therefore it is likely that uncontrolled asthma during pregnancy can carry additional risks for offspring asthma along with conferring a genetic risk.

At present, only one study has focused on the severity and control of asthma during pregnancy and offspring asthma risk, showing a higher risk of asthma among children of mothers with moderate-to-severe uncontrolled asthma than those of mothers with mild controlled asthma.[13] However, this study was underpowered to provide precise estimates for the influence of maternal moderate-to-severe controlled asthma. Moreover, it is becoming increasingly evident that asthma is not a single disorder but a syndrome encompassing several phenotypes, which can have distinct pathogeneses,[14] and be associated with risk factors differently.[15,16] For instance, early-onset persistent asthma is more strongly affected by early-life environmental exposure than other phenotypes of asthma.[15,16]

In the present study we aimed to investigate the association between asthma severity and control during pregnancy and the risk of 3 phenotypes of asthma in the offspring. We hypothesized that children of mothers with uncontrolled asthma had higher asthma risk, in particular early-onset persistent asthma compared with those of mothers with mild controlled asthma.

METHODS

Study population

The study was a population-based cohort study built on Danish national registers. All liveborn and new residents in Denmark are assigned a unique

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Abbreviations used
ATC: Anatomical Therapeutic Chemical
ICD-8: International Classification of Diseases, 8th Revision
ICD-10: International Classification of Diseases, 10th Edition
PR: Prevalence ratio

10-digit identifier recorded in the Danish Civil Registration System.[17] The identifier enables us to link individual-level data between and within all national registers. We first identified 694,770 liveborn singletons during 1996-2006 from the Danish Medical Birth Registry.[18] We excluded 4,372 children with missing or likely errors in gestational age (<154 or >315 days). Because our outcomes of interest were measured according to asthma treatment at the ages of 0 to 3 and 4 to 6 years, to ensure all children were followed until age 6 years, we excluded a further 11,643 children who emigrated and 3,376 children who died before their 6th birthday (Fig 1). Altogether, 675,379 singletons were included in our analyses.

Maternal asthma history before delivery. We defined maternal asthma as at least 1 inpatient, outpatient, or emergency department visit for asthma before delivery from the Danish National Patient Register.[19] The register contains data on inpatient contacts since 1977 and, from 1995, also emergency department and outpatient treatments. International Classification of Diseases, 8th Revision (ICD-8), codes were used from 1977-1993, and International Classification of Diseases, 10th Edition (ICD-10), codes were used from 1994 and onward. Information on maternal asthma was identified based on ICD-8 code 493 and ICD-10 codes J45 or J46. We similarly defined paternal asthma history.

Active asthma during pregnancy. Asthmatic mothers were categorized as having active asthma if they redeemed at least 1 antiasthma medication prescription or had 1 or more inpatient, outpatient, or emergency department visit for asthma during the index pregnancy. Pregnancy was counted from the first day of the last menstrual period until delivery. Information on antiasthma medication prescriptions was obtained from the Danish National Prescription Registry,[20] which covers all prescriptions dispensed in Denmark since 1995. It contains the Anatomical Therapeutic Chemical (ATC) classification codes, the number of defined daily dose per package, the number of packages dispensed, and the dispensation date. The ATC codes for antiasthma medication were for inhaled β_2-agonists (R03AC02-04, R03AC12, and R03AC13), inhaled glucocorticoids (R03BA01, R03BA02, and R03BA05), fixed-dose combination of inhaled β_2-agonists and glucocorticoids (R03AK06 and R03AK07), leukotriene receptor antagonists (R03DC03), and anti-IgE treatment (R03DX05).

Asthma severity and control during pregnancy. Information on the severity and control of active asthma during pregnancy was obtained from the Danish National Prescription Registry and the Danish National Patient Register.[19,20] We defined asthma severity and control on the basis of the doses of inhaled corticosteroids (in beclomethasone-chlorofluorocarbon equivalents), add-on therapy (theophylline, long-acting β_2-agonists, and leukotriene receptor antagonists), short-acting β_2-agonist doses per week, and moderate-to-severe exacerbation (defined as inpatient treatment, emergency department visit for asthma, or a filled prescription of an oral corticosteroid).[21] The following ATC codes were used: theophylline (R03DA04), long-term acting β_2-agonists (R03AC12 and R03AC13), short-acting β_2-agonists (R03AC02-04), and oral corticosteroid (H02AB). The number of days exposed per prescription of a specific drug was calculated by multiplying the number of defined daily dose per package by the number of packages dispensed. The number of days exposed to a specific drug was calculated by adding all prescriptions' durations. The equivalence of the average daily dosage of inhaled corticosteroids into beclomethasone-chlorofluorocarbon equivalents was calculated according to the equivalency table generated by the Canadian Asthma Consensus Guidelines.[22] We created 4 mutually exclusive groups according to the various combinations of maternal asthma severity and control, as described below: (1) mild controlled, (2) mild uncontrolled, (3) moderate-to-severe controlled, and (4) moderate-to-severe uncontrolled asthma (see Table E1 in this article's Online Repository at www.jacionline.org). The definitions of asthma severity and control have been described in detail elsewhere.[21]

Asthma severity. We defined *mild asthma* as treatment with inhaled glucocorticoid doses of 251 to 500 μg/d with no add-on therapy or inhaled glucocorticoid doses of 0 to 250 μg/d regardless of add-on therapy. To be categorized as mild asthma, the following situations were not included: (1) moderate-to-severe exacerbations and 4 to 10 doses of short-acting β_2-agonists per week or (2) more than 10 doses of short-acting β_2-agonists per week. We defined *moderate-to-severe asthma* as treatment with inhaled glucocorticoids doses of 251 to 500 μg/d with add-on therapy or inhaled glucocorticoid doses of greater than 500 μg/d.

Asthma control. Asthmatic mothers were considered as having *controlled asthma* if they had no moderate-to-severe exacerbations and were taking 0 to 3 doses of short-acting β_2-agonists per week for mild asthma and 10 or less doses of short-acting β_2-agonists per week for moderate-to-severe asthma. Moreover, a woman was considered to have *moderate-to-severe uncontrolled asthma* if she had one of the following situations: (1) moderate-to-severe exacerbations and 4 to 10 doses of short-acting β_2-agonists per week or (2) greater than 10 doses of short-acting β_2-agonists per week.

Childhood asthma in offspring: outcomes of interest

Our outcomes of interest were 3 mutually exclusive phenotypes of asthma in the offspring according to asthma treatment (ie, hospital or antiasthma treatment) during 0 to 3 years and 4 to 6 years based on schema from Martinez et al[14]:

1. *early-onset transient asthma:* asthma treatment during 0 to 3 years but no treatment during 4 to 6 years;
2. *early-onset persistent asthma*: asthma treatment during both 0 to 3 years and 4-6 years; and
3. *late-onset asthma*: no asthma treatment during 0 to 3 years but with treatment during 4 to 6 years.

Asthma hospital treatment was defined as having an inpatient, outpatient, or emergency department visit for asthma (ICD-10 codes J45 and J46) retrieved from the Danish National Patient Register. Antiasthma treatment was defined as 2 or more dispensed prescriptions of an antiasthma medication mentioned above within 1 year by using the Danish National Prescription Registry. We defined asthma treatment during age 0 to 3 years as at least 2 prescriptions of an antiasthma medication within 1 year or at least 1 hospital treatment for asthma during 0 to 3 years. We similarly defined asthma treatment during age 4 to 6 years.

Statistical analysis

Statistical analyses were done with SAS 9.4 software (SAS Institute, Cary, NC). We calculated the prevalence of each phenotype of asthma: early-onset transient, early-onset persistent, and late-onset asthma. Because asthma is not a rare outcome, we estimated the prevalence ratio (PR) of each phenotype of asthma and their 95% CIs by using a log-binomial model.[23] The log-binomial method was performed with PROC GENMOD by using binomial distribution and the log link. We specified an initial value of −4 for the intercept. A woman can contribute more than 1 pregnancy to the analysis. We used a robust sandwich variance estimator for correction of SEs to account for the dependence between siblings. A P value of less than .05 (2-sided test) was considered statistically significant. We included missing values as separate groups in the models. We adjusted for the following covariates: maternal age (<25, 25-34, or ≥35 years), calendar year of birth (1996-1999, 2000-2003, or 2004-2006), parity (first/second or higher), maternal smoking during pregnancy (yes/no), place of residence (capital or capital suburb, provincial city or town, or rural areas), income status (lowest quartile/above lowest quartile), education (elementary school/above elementary school), and paternal asthma (yes/no) at the time of childbirth. Data on these covariates were extracted from the registers mentioned above, as well as from Statistics Denmark's registers on socioeconomic status.[24] Death of a close relative (a child, partner/spouse, a parent, or a sibling) is considered one of the most stressful life