Original Article

Adverse Pregnancy Outcomes in Asthmatic Women: A Population-Based Family Design Study

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What is already known about this topic? Asthma affects a large proportion of pregnant women worldwide and is associated with adverse outcomes. Unknown and unmeasurable confounders might play a role in the association between asthma and adverse pregnancy and delivery outcomes.

What does this article add to our knowledge? We found that the association between asthma and adverse pregnancy, delivery, and perinatal outcomes remained after adjusting for genetic and environmental factors shared by siblings and cousins.

How does this study impact current management guidelines? Maternal asthma continues to be an important clinical target to diminish risks of adverse pregnancy, delivery, and perinatal outcomes.

BACKGROUND: Asthma is associated with several adverse pregnancy and perinatal outcomes. Familial factors may confound these associations.

OBJECTIVE: To examine the role of measured and unmeasured confounding by conducting a study that compared differentially exposed cousins and siblings from the same families.

METHODS: We retrieved data on adverse pregnancy outcomes, prescribed drugs, and physician-diagnosed asthma from nationwide registers for all women in Sweden with singleton births between 2001 and 2013. Logistic and linear regression estimated the association between maternal asthma and several outcomes in the whole population and within differently exposed pregnant relatives.

RESULTS: In total, 1,075,153 eligible pregnancies were included and 10.1% of the study population had asthma. We identified 475,200 cousin and 341,205 sister pregnancies. Women with asthma had increased risks for preeclampsia (adjusted odds ratio [aOR], 1.17; 95% CI, 1.13-1.21), emergency cesarean section (aOR, 1.24; 95% CI, 1.22-1.27), and having a child small for gestational age (aOR, 1.18; 95% CI, 1.12-1.23). In the conditional regression analyses, after adjustment for familial factors, the associations remained: preeclampsia in cousins (aOR, 1.16; 95% CI, 1.07-1.25) and siblings (aOR, 1.23; 95% CI, 1.08-1.38), emergency cesarean section in cousins (aOR, 1.28) and siblings (aOR, 1.21), and small for gestational age in cousins (aOR, 1.17) and siblings (aOR, 1.13).

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Abbreviations used
aOR- Adjusted odds ratio

CONCLUSIONS: Factors shared by siblings and cousins do not seem to explain the observed association between maternal asthma and adverse pregnancy outcomes. This implies that targeting the asthma disease will continue to be important in reducing risks for adverse outcomes in pregnancy. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Asthma; Epidemiology; Family design; Pregnancy; Pregnancy outcomes*

Asthma is a common disease that affects a large proportion of the population; its prevalence is estimated to be 8% to 10% among women of childbearing age.[1,2] There are substantial genetic influences on asthma in the adult population,[3] and shared environmental factors, such as family size, smoking, socioeconomic status, and health management behavior, have also been shown to play a role in the development of the disease in adults.[4-6] Previous studies have shown increased risks of several adverse pregnancy and delivery outcomes in women with asthma[7,8] and in a large population-based study we recently found associations between asthma in pregnant women and several adverse pregnancy, delivery, and birth outcomes, regardless of the level of asthma control.[9] However, it is not known to what extent genetic and familial environmental factors play a role for these adverse outcomes in women with asthma.

To account for some of these unmeasured possible confounders, it is possible to use a quasi-experimental design with cousin/sibling controls. This family-based design allows for adjustments for all factors shared between siblings or cousins. If such analyses show an equally strong association after these adjustments, the exposure studied (in this case maternal asthma) is a potential causal risk factor for the outcome. If the association weakens compared with that based on unrelated controls, it is likely that familial factors have confounded the observed association. A family-based design does not confirm causality, but it gives stronger support of a casual effect compared with ordinary observational studies because it is possible to adjust for some important unmeasured, unmeasurable, or unknown confounders.[10-13]

Our hypothesis was that maternal asthma is causally related to adverse pregnancy outcomes such as preeclampsia or eclampsia, placental abruption, delivery mode, birth weight, and gestational age. To test our hypothesis rigorously, we adjusted for measured covariates as well as unmeasured genetic and shared familial factors by conducting a register- based study, with sibling and cousin control designs, based on all women who gave birth in Sweden during the period 2001 to 2013.

METHODS

Study design and population

This population-based study was conducted using several Swedish health and population registers. The registers were linked using the unique personal identification number assigned to all permanent residents of Sweden.[14] We used the Swedish Medical Birth Register,[15,16] covering approximately 99% of all births in Sweden, to identify all women giving birth in the years 2001 to 2013. In a second step, we linked these women to the Multi Generation Register[17] to identify full sisters and full cousins. In addition, we used information from the National Patient Register, which covers all inpatient care in Sweden since 1987 and 75% of all outpatient visits from 2001,[18] and the Swedish Prescribed Drug Register, which contains all prescribed drugs dispensed at pharmacies in Sweden since July 1, 2005.[19] The use of a prescription for asthma medication in the Swedish Prescribed Drug Register as a proxy for asthma disease has been validated previously.[20]

We excluded multiple gestation pregnancies because their characteristics often differ from those in singleton pregnancies, making any observed associations difficult to interpret.[21] Permission for this study was obtained from the Regional Ethical Review board in Stockholm, Sweden (reference 2014/2037-32). In accordance with their decision, we did not obtain informed consent from participants involved in the study. All data were deidentified before analyses.

Exposure

Our exposure was maternal asthma from the age of 15 years until delivery. Information on asthma was collected from 3 different sources: the National Patient Register; the Medical Birth Register with information on pregnancy, delivery, and perinatal outcomes and diagnoses recorded at antenatal visits and delivery wards; and records of asthma medication from the Swedish Prescribed Drug Register. From the National Patient Register and the Medical Birth Register we identified asthma diagnoses (code 493 according to the *International Classification of Diseases, Ninth Revison*, and codes J45 and J46 according to the *International Classification of Diseases, Tenth Revison*). From the Medical Birth Register, we collected data on whether the mother had ever had asthma (a question asked by the midwife in early pregnancy and present as a tick-box), and from the Prescribed Drug Register, for women being pregnant from July 1, 2006, we identified all those who had asthma medication dispensed at least twice from the year before pregnancy until delivery (Anatomical Therapeutic Chemical Classification System codes R03AC, R03AK, R03BA, and R03DC).

Outcome

The outcome data (pregnancy, delivery, and perinatal complications and diagnoses) were collected from the Medical Birth Register based on the *International Classification of Diseases, Tenth Revison* codes for preeclampsia/eclampsia (O14-15) and placental abruption (O45). We also assessed the mode of delivery and several birth outcomes (birth weight and gestational age as well as small and large for gestational age[22]).

Covariates

Possible confounders were selected using directed acyclic graphs[23] and collected from the Medical Birth Register (smoking [none/1-9 cigarettes/≥10 cigarettes per day], body mass index, civil status [married or cohabiting/single/other situations], and the participant's country of birth [Sweden/other Scandinavian countries/rest of the world]). All data used from the Medical Birth Register were reported at the first antenatal visit. There are data on body mass index and smoking during pregnancy as well but those data are not as reliable. Socioeconomic status, defined as the highest level of education, was extracted from the longitudinal integration database for health insurance and labor market studies (LISA by Swedish acronym)