

Original Article

Exposure to Allergen-Specific Immunotherapy in Pregnancy and Risk of Congenital Malformations and Other Adverse Pregnancy Outcomes

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What is already known about this topic? A few studies examined the administration of allergen-specific immunotherapy (AIT) in pregnant women and report an absence of elevated risk of adverse pregnancy outcomes. However, earlier studies were small and guidelines continue to recommend against initiating AIT during pregnancy.

What does this article add to our knowledge? In this nationwide population-based study, we compared 743 pregnancies exposed to AIT and more than 900,000 pregnancies without a record of AIT. We found no association between AIT in pregnancy and congenital malformations or other adverse pregnancy outcomes.

How does this study impact current management guidelines? We believe these findings will help both physicians and pregnant women make informed decisions about AIT in pregnancy.

BACKGROUND: Owing to insufficient data, current guidelines recommend against initiating allergen-specific immunotherapy (AIT) during pregnancy but suggest that well-tolerated ongoing immunotherapy may be continued.

OBJECTIVE: To evaluate the safety of AIT in pregnancy, especially the risk for congenital malformations.

METHODS: This nationwide Swedish cohort study identified pregnancies exposed to AIT, both subcutaneous and sublingual, through the Swedish Medical Birth register and the Prescribed Drug Register between 2005 and 2014. Information on congenital malformations in offspring was retrieved from the National Patient Register. Using the personal identity number, we linked data between registers. Using logistic regression, we calculated odds ratios (ORs) with 95% CIs for congenital malformations and other adverse pregnancy outcomes after adjusting for potential confounders.

RESULTS: From 2005 to 2014, we identified 924,790 singleton pregnancies. Among these, 743 pregnancies had been exposed to AIT 3 months before conception up until gestational week 22. Allergen-specific immunotherapy in pregnancy was not linked to

congenital malformations (OR = 0.90; 95% CI, 0.63-1.27) or other adverse pregnancy outcomes (preterm birth: OR = 0.98; 95% CI, 0.71-1.35; stillbirth: OR = 0.79; 95% CI, 0.26-2.47; or cesarean delivery: OR = 0.91; 95% CI, 0.76-1.09). Stratification by route of immunotherapy, subcutaneous or sublingual, resulted in similar ORs. Restricting the pregnancy cohort to women with asthma or pulmonary disease, nulliparous women, births in 2012 to 2014, or Swedish-born women yielded similar results.

CONCLUSIONS: This nationwide study found no evidence of congenital malformations or other adverse pregnancy outcomes in women treated with AIT in pregnancy. © 2022 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2022;■:■-■)

Key words: Allergen-specific immunotherapy; Congenital malformations; Adverse pregnancy outcomes; Epidemiology

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Abbreviations used

AIT- Allergen-specific immunotherapy
 MBR- Medical Birth Register
 NPR- National Patient Register
 PDR- Prescribed Drug Register
 SCIT- Subcutaneous immunotherapy
 SGA- Small for gestational age
 SLIT- Sublingual immunotherapy
 VIT- Venom immunotherapy

INTRODUCTION

Long-term immune tolerance against environmental allergens can be achieved through allergen-specific immunotherapy (AIT), the repeated administration of specific allergens to individuals with IgE-mediated diseases to initiate tolerance and protect against allergic symptoms and adverse reactions associated with exposure to these allergens.¹ The secondary prevention of new allergic sensitizations and progression to more severe disease and comorbidity is a key benefit of AIT-induced clinical tolerance.²⁻⁴ For over a century, AIT has been used worldwide as a desensitizing therapy for allergy-related disease.⁵ Allergen-specific immunotherapy is available mainly by sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) routes and typically carries on for 3 to 5 years to promote long-term symptom remission. To date, immunotherapy represents the only curative and specific method of treatment that targets the underlying immunologic mechanisms of IgE-mediated diseases.^{6,7}

Asthma and allergic rhinitis are frequent in pregnancy.⁸ Of major importance to treating these conditions during pregnancy is evidence of fetal hazard, although maternal health should also be considered when optimizing treatment. Immune intervention in terms of AIT can control symptoms that have a potential direct or indirect effect on the health of both mother and fetus by preventing exacerbations of uncontrolled asthma and allergic rhinitis. A few studies examined the administration of AIT during pregnancy; they reported no association with spontaneous abortion, preeclampsia, preterm birth, or congenital malformations.⁹⁻¹¹ However, because of scarce safety data and the potential risk for anaphylaxis complicating AIT, initiation during pregnancy is still not recommended, although well-tolerated ongoing AIT may be maintained.^{1,12,13}

This nationwide cohort study aimed to investigate the association between AIT in pregnancy and the risk for congenital malformations and other adverse pregnancy outcomes between 2005 and 2014 in Sweden.

METHODS**Study design and population**

We conducted a population-based cohort study using prospectively collected data from nationwide Swedish health care registers to assess the risk for congenital malformations and other adverse pregnancy outcomes in women who received AIT during pregnancy in 2005 to 2014.

The registers

The Swedish Medical Birth Register (MBR) was established in 1973 and includes data on nearly all births in Sweden. Information on pregnancy and delivery is collected prospectively by midwives using standardized medical records in perinatal care.¹⁴

Founded in 1964, the Swedish National Patient Register (NPR) achieved nationwide coverage for inpatient diagnoses in 1987; information on outpatient visits has been available since 2001. The Swedish International Classification of Disease coding system is used to code diagnostic data.¹⁵

The Swedish Prescribed Drug Register (PDR) was established in 2005 and is a nationwide database that contains all prescribed drugs dispensed at pharmacies. The purpose of the register is to increase patient safety in the pharmaceutical area.¹⁶ Allocated at birth to all residents in Sweden, the personal identity number links data among national registers for research purposes after ethics approval.^{17,18}

Study population

Through the MBR, we identified all pregnancies in Sweden with both a conception date and delivery date between January 1, 2005, and December 31, 2014. We retrieved data on infant sex, mode of delivery, stillbirth, gestational age, birth weight, Apgar score at 5 minutes, and maternal factors (see covariates, discussed subsequently). We identified pregnancies with at least one record of SCIT or SLIT in the NPR 3 months before conception up to gestational week 22 in 2005 to 2014. We limited exposure up until gestational week 22 because we primarily aimed to study congenital malformations. Congenital malformations occur during the first trimester, whereas a later record of AIT would make stillbirth and preterm birth impossible until the date of exposure (eg, in women with a record of AIT in gestational week 37, preterm birth as an outcome would be unfeasible). Sublingual immunotherapy to treat grass pollen seasonal allergy was launched in 2005 in Sweden. Therefore, we restricted the study cohort to pregnancies conceived in 2005 or later. All analyses, except stillbirth analyses, were restricted to live births.

Maternal covariates

Through the Swedish MBR, we retrieved data on maternal age at delivery (age 24 years or less, 25 to 29 years, 30 to 34 years, and 35 years and greater), country of birth (Sweden, other Nordic countries, Europe [but not the Nordic countries], Africa, Asia, North America, South America, the former Soviet Union, Oceania, unknown country, or missing), parental cohabitation (yes/no, or missing), education (9 years or less, 10 to 12 years, greater than 12 years, or missing), nulliparous (yes or no), body mass index based on height and weight measured in early pregnancy (less than 18.5, 18.5 to 24.99, 25 to 29.99, 30 to 34.99, 35 to 39.99, 40 or greater, or missing), self-reported smoking habits at first antenatal visit (nonsmoker, one to nine cigarettes per day, 10 or more cigarettes per day, or missing), asthma or pulmonary disease (yes or no), and calendar period of birth (2005 to 2008, 2009 to 2011, or 2012 to 2014).

Exposure

Through Swedish national registers, we identified women with records of SCIT or SLIT 3 months before conception until gestational week 22 during 2005 to 2014. We defined exposure as having a relevant medical procedure code for SCIT (DT001 or DT029) in the NPR, or the Anatomical Therapeutic Chemical code for grass pollen SLIT (V01AA02) in the PDR.

TABLE I. Demographic characteristics of pregnancies exposed to subcutaneous or sublingual allergen-specific immunotherapy (AIT) in 2005 to 2014 in Sweden compared with unexposed pregnancies

Characteristics	Pregnancies unexposed to AIT, n (%)	Pregnancies exposed to AIT, n (%)
n	924,047	743
Infant sex		
Female	448,836 (48.6)	375 (50.5)
Male	475,206 (51.4)	368 (49.5)
Calendar period of birth		
2005-2008	278,398 (30.1)	176 (23.7)
2009-2011	320,836 (34.7)	258 (34.7)
2012-2014	324,812 (35.2)	309 (41.6)
Maternal age at delivery, y		
<24	134,555 (14.6)	61 (8.2)
25-29	269,485 (29.2)	226 (30.4)
30-34	318,232 (34.4)	298 (40.1)
≥35	201,775 (21.8)	158 (21.3)
Maternal country of birth		
Sweden	705,848 (76.4)	650 (87.5)
Nordic (not Sweden)	13,257 (1.4)	5 (0.7)
Europe (not Nordic)	55,244 (6.0)	21 (2.8)
Africa	33,727 (3.6)	9 (1.2)
Asia	93,598 (10.1)	37 (5.0)
North America	4,017 (0.4)	2 (0.3)
South America	10,184 (1.1)	13 (1.7)
Former Soviet Union	418 (0.0)	0
Oceania	466 (0.1)	0
Unknown country	5,580 (0.6)	4 (0.5)
Missing	1,708 (0.2)	2 (0.3)
Living with partner		
Yes	827,630 (89.6)	655 (88.2)
No	55,434 (6.0)	31 (4.2)
Missing	40,983 (4.4)	57 (7.7)
Education, y		
≥12	495,507 (53.6)	528 (71.1)
10-12	334,775 (36.2)	208 (28.0)
≤9	85,138 (9.2)	7 (0.9)
Missing	8,627 (0.9)	0
Nulliparous		
No	513,868 (55.6)	325 (43.7)
Yes	410,179 (44.4)	418 (56.3)
Body mass index		
Underweight (<18.5)	21,189 (2.3)	10 (1.3)
Normal weight (18.5-24.99)	516,804 (55.9)	432 (58.1)
Overweight (25-29.99)	216,151 (23.4)	158 (21.3)
Class I obese (30-34.99)	74,508 (8.1)	51 (6.9)
Class II obese (35-39.99)	23,189 (2.5)	9 (1.2)
Class III obese (≥40)	8,428 (0.9)	8 (1.1)
Missing	63,778 (6.9)	75 (10.1)
Early pregnancy smoking habits		
Nonsmoker	830,138 (89.8)	674 (90.7)
1-9 cigarettes/d	44,192 (4.8)	10 (1.3)
≥10 cigarettes/d	12,645 (1.4)	1 (0.1)
Missing	37,072 (4.0)	58 (7.8)

(continued)

TABLE I. (Continued)

Characteristics	Pregnancies unexposed to AIT, n (%)	Pregnancies exposed to AIT, n (%)
Maternal asthma or pulmonary disease		
No	856,328 (92.7)	457 (61.5)
Yes	67,719 (7.3)	286 (38.5)

Outcome

The main outcome was congenital malformations. Secondary outcomes were other adverse pregnancy outcomes, especially preterm birth, stillbirth, and cesarean delivery, both elective and emergency. Congenital malformations were defined according to the European Network of population-based registries for the epidemiologic surveillance of congenital anomalies classification.¹⁹ Relevant International Classification of Diseases-10 codes were used: roughly Q00 to Q99 with modifications (see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org). Cesarean delivery was categorized as elective when it occurred before the onset of labor, or as an emergency. Preterm birth was defined as birth before 37 weeks of gestation. Stillbirth was defined as the delivery of a dead fetus at 28 completed weeks of gestation or earlier up until June 30, 2008, and since July 1, 2008, as the delivery of a dead fetus at 22 gestational weeks or earlier. Small for gestational age (SGA) was defined as birth weight less than the 10th percentile for children of similar sex and gestational age, according to the Swedish reference curve of estimated fetal growth, whereas large for gestational age was defined as birth weight greater than the 90th percentile.²⁰ Finally, a low Apgar score was defined as less than 7 at 5 minutes.

Statistical analyses

We used logistic regression analysis to estimate crude and adjusted odds ratios (ORs) with 95% CIs for the association between AIT during pregnancy and congenital malformations or other adverse pregnancy outcomes. We adjusted for infant sex, calendar period of birth, and maternal factors such as age at delivery, country of birth, parental cohabitation, education, parity, body mass index, smoking during pregnancy, and asthma or pulmonary disease. In a separate analysis, we divided data by route of immunotherapy, SCIT or SLIT. We further examined the risk for congenital malformations and other adverse pregnancy outcomes in women with asthma or pulmonary disease who received AIT in pregnancy. In additional analyses, we restricted the cohort to nulliparous women with records of AIT, a calendar period of birth in 2012 to 2014, Swedish-born AIT-treated pregnant women, or women with records of AIT first appearing during pregnancy.

We used SPSS software (version 25.0, SPSS, Inc, Chicago, Ill) for statistical analysis. Odd ratios with 95% CIs that did not include 1.0 were considered statistically significant.

Ethics

This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr. 2008/1182-31/4). The board waived informed consent because of the strict register-based nature of the study.²¹

RESULTS

Among 924,790 singleton livebirth pregnancies between 2005 and 2014 in Sweden, we identified 743 exposed to AIT 3

TABLE II. Crude and adjusted odds ratios (ORs) for adverse pregnancy outcomes in pregnancies exposed to subcutaneous or sublingual allergen-specific immunotherapy (AIT) in 2005 to 2014

Adverse pregnancy outcomes	Exposed to AIT: observed events/total (%)	Unexposed to AIT: observed events/total (%)	Crude OR; 95% CI	Adjusted OR; 95% CI
Caesarean delivery	148/743 (19.9)	155,549/924,047 (16.8)	0.81; 0.68-0.97	0.91-0.76-1.09
Elective	68/743 (9.2)	79,054/924,047 (8.6)	0.93; 0.72-1.19	0.98; 0.77-1.27
Emergency	80/743 (10.8)	76,496/924,047 (8.3)	0.75; 0.59-0.94	0.86; 0.68-1.09
Preterm birth (<37 wk)	39/743 (5.2)	44,629/924,047 (4.8)	0.92; 0.66-1.27	0.98; 0.71-1.35
Congenital malformations	33/743 (4.4)	35,998/924,047 (3.9)	0.87; 0.62-1.24	0.90; 0.63-1.27
Stillbirth	3/746 (0.4)	3019/927,066 (0.3)	0.81; 0.26-2.52	0.79; 0.26-2.47
Fetal growth				
Small for gestational age	69/743 (9.3)	85,278/922,318 (9.2)	1.00; 0.78-1.28	0.97; 0.75-1.24
Large for gestational age	77/743 (10.4)	91,972/922,318 (10.0)	0.96; 0.76-1.21	0.92; 0.73-1.18
Low Apgar score (<7) at 5 min	9/743 (1.2)	10,772/924,047 (1.2)	0.96; 0.50-1.86	1.04; 0.54-2.01

Crude and adjusted ORs were adjusted for infant sex, calendar period of birth, maternal age at delivery, maternal country of birth, living with partner, education, parity, body mass index, early pregnancy smoking, and maternal asthma or pulmonary disease.

months before conception up until gestational week 22. [Table I](#) lists the demographic characteristics of pregnant women exposed to AIT. Compared with unexposed pregnancies, those with records of AIT were generally of higher age (40.1% of AIT-treated pregnant women were from age 30 to 34 years at delivery compared with 34.4% of untreated ones) and education (education greater than 12 years in 71.1% of AIT-treated women vs 53.6% of untreated ones), were nulliparous (56.3% vs 44.4%), were born in Sweden (87% vs 76.4%), a higher proportion had self-reported asthma or pulmonary disease (38.5% vs 7.3%), and belonged to calendar period of birth 2012 to 2014 (41.6% vs 35.2%). Median maternal age at delivery was 31.0 years (interquartile range, 6 years) for women who received AIT during pregnancy; and 30.0 years (interquartile range, 7 years) for those with no records of AIT.

During the 2005 to 2014 study period, 3,022 stillbirths were observed in addition to live births, for a total of 927,812 registered pregnancies.

Congenital malformations. Of 743 pregnancies exposed to AIT, 33 had a congenital malformation (4.4%), compared with 35,998 of 924,047 women without AIT (3.9%). This translated into a nonsignificant adjusted OR of 0.90 (95% CI, 0.63-1.27) for congenital malformations ([Table II](#)).

Other adverse pregnancy outcomes. Allergen-specific immunotherapy was not associated with other adverse pregnancy outcomes; preterm birth: OR = 0.98 (95% CI, 0.71-1.35); stillbirth: OR = 0.79 (95% CI, 0.26-2.47); cesarean delivery: OR = 0.91 (95% CI, 0.76-1.09); elective: OR = 0.98 (95% CI, 0.77-1.27); or emergency: OR = 0.86 (95% CI, 0.68-1.09) ([Table II](#)).

Subanalyses

In separate analyses, we stratified by route of immunotherapy SCIT (n = 563) or SLIT (n = 204), which resulted in similar ORs ([Table III](#)). For instance, the ORs for congenital malformations were 0.80 (95% CI, 0.54-1.17) and 1.38 (95% CI, 0.61-3.10), respectively). Restricting the pregnancy cohort to women with asthma or pulmonary disease, nulliparous women, or births in 2012 to 2014 yielded similar results ([Tables IV-VI](#)).

Further analyses limited to Swedish-born women are presented in [Table E1](#) (in this article's Online Repository at www.jaci-inpractice.org). Analyses based on 165 women with records of AIT first appearing during pregnancy resulted in a decreased risk for congenital malformations (OR = 0.53; 95% CI, 0.29-0.94), preterm birth (OR = 0.53; 95% CI, 0.31-0.91), and low Apgar score (less than 7) at 5 minutes (OR = 0.28; 95% CI, 0.13-0.60), whereas risk estimates for the other pregnancy outcomes did not change (see [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This population-based Swedish register study using prospectively collected data found no association between AIT in pregnancy and congenital malformations or other adverse pregnancy outcomes. Thus, we confirm the negative findings of several smaller retrospective studies.^{9,10} In 1978, Metzger et al¹⁰ examined the safety of AIT during pregnancy and suggested that SCIT administration was not associated with congenital malformations or other pregnancy outcomes, whereas a higher incidence of miscarriage was seen in untreated pregnant women with atopy. In addition, the occurrence of allergic disease in the offspring of AIT-treated pregnant women did not differ from that of children with allergic heredity. Notably, in 1993, another retrospective study reported that the incidence of spontaneous abortion, preeclampsia, and preterm birth was higher in a group of women who refused AIT compared with a group of SCIT-treated pregnant women. In that study,⁹ the frequency of complications in pregnant women who received SCIT was similar to that in the general population.

In 2012, a prospective study found that compared with conventional pharmacotherapy, SLIT administration during pregnancy did not lead to unfavorable outcomes including abortion, preeclampsia, preterm birth, or perinatal death.¹¹ Although the study was prospective, no randomization was performed because patients were allowed to choose the treatment method. In the intervention group, 155 pregnant patients maintained SLIT, or in one-sixth of cases they initiated it, during 185 pregnancies, whereas the two control groups received either budesonide 400 µg twice daily (85 patients) or rescue salbutamol inhalation when needed

TABLE III. Crude and adjusted odds ratios (ORs) for adverse pregnancy outcomes in pregnancies exposed to subcutaneous allergen-specific immunotherapy (SCIT) or sublingual allergen-specific immunotherapy (SLIT) in 2005 to 2014

Adverse pregnancy outcomes	SCIT during pregnancy: crude OR; 95% CI (n = 563)	SCIT during pregnancy: adjusted OR; 95% CI (n = 563)	SLIT during pregnancy: crude OR; 95% CI (n = 204)	SLIT during pregnancy: adjusted OR; 95% CI (n = 204)
Caesarean delivery	0.75; 0.61-0.91	0.83; 0.68-1.02	1.05; 0.72-1.52	1.21; 0.83-1.76
Elective	0.90; 0.68-1.20	0.95; 0.72-1.23	1.10; 0.66-1.83	1.18; 0.71-1.98
Emergency	0.67; 0.52-0.86	0.77; 0.59-0.99	0.99; 0.60-1.63	1.19; 0.72-1.97
Preterm birth (<37 wk)	0.90; 0.62-1.30	0.96; 0.66-1.39	0.99; 0.52-1.86	1.07; 0.57-2.02
Congenital malformations	0.77; 0.53-1.13	0.80; 0.54-1.17	1.34; 0.59-3.01	1.38; 0.61-3.10
Stillbirth	1.84; 0.26-13.09	1.81; 0.25-12.89	0.33; 0.08-1.34	0.33; 0.08-1.33
Fetal growth				
Small for gestational age	0.96; 0.73-1.27	0.93; 0.70-1.23	0.99; 0.62-1.59	0.99; 0.61-1.59
Large for gestational age	0.93; 0.71-1.21	0.92; 0.70-1.21	1.08; 0.67-1.73	0.97; 0.60-1.57
Low Apgar score (<7) at 5 min	0.73; 0.38-1.40	0.79; 0.41-1.53	Omitted	Omitted

Crude and adjusted ORs were adjusted for infant sex, calendar period of birth, maternal age at delivery, maternal country of birth, living with partner, education, parity, body mass index, early pregnancy smoking, and maternal asthma or pulmonary disease.

TABLE IV. Women with asthma or pulmonary disease: crude and adjusted odds ratios (ORs) for adverse pregnancy outcomes in pregnancies exposed to allergen-specific immunotherapy (subcutaneous or sublingual) in 2005 to 2014

Adverse pregnancy outcomes	Women with asthma or pulmonary disease (crude OR; 95% CI) (n = 68,005)	Women with asthma or pulmonary disease (adjusted OR; 95% CI) (n = 68,005)
Caesarean delivery	0.86; 0.65-1.14	0.88; 0.66-1.17
Elective	0.95; 0.65-1.38	0.91; 0.62-1.33
Emergency	0.81; 0.56-1.16	0.88; 0.61-1.27
Preterm birth (<37 wk)	0.89; 0.55-1.46	0.84; 0.52-1.38
Congenital malformations	1.19; 0.63-2.24	1.20; 0.64-2.26
Stillbirth	0.97; 0.14-6.92	0.96; 0.13-6.89
Fetal growth		
Small for gestational age	0.81; 0.57-1.17	0.78; 0.54-1.12
Large for gestational age	1.55; 0.98-2.44	1.44; 0.91-2.28
Low Apgar score (<7) at 5 min	3.86; 0.54-27.53	3.96; 0.56-28.29

Crude and adjusted ORs were adjusted for infant sex, calendar period of birth, maternal age at delivery, maternal country of birth, living with partner, education, parity, body mass index, and early pregnancy smoking. Analyses were based on 68,005 women with asthma or pulmonary disease.

TABLE V. Nulliparous women: crude and adjusted odds ratios (ORs) for adverse pregnancy outcomes in pregnancies exposed to allergen-specific immunotherapy (subcutaneous or sublingual) in 2005 to 2014

Adverse pregnancy outcomes	Nulliparous women (crude OR; 95% CI) (n = 410,597)	Nulliparous women (adjusted OR; 95% CI) (n = 410,597)
Caesarean delivery	0.96; 0.75-1.23	1.02; 0.79-1.30
Elective	0.99; 0.68-1.46	1.09; 0.74-1.60
Emergency	0.95; 0.71-1.27	0.98; 0.73-1.31
Preterm birth (<37 wk)	0.87; 0.59-1.28	0.90; 0.61-1.32
Congenital malformations	0.93; 0.58-1.49	0.95; 0.59-1.52
Stillbirth	Omitted	Omitted
Fetal growth		
Small for gestational age	0.97; 0.73-1.29	0.88; 0.66-1.17
Large for gestational age	0.84; 0.58-1.22	0.86; 0.59-1.25
Low Apgar score (<7) at 5 min	1.07; 0.48-2.40	1.11; 0.49-2.49

Crude and adjusted ORs were adjusted for infant sex, calendar period of birth, maternal age at delivery, maternal country of birth, living with partner, education, body mass index, early pregnancy smoking, and maternal asthma or pulmonary disease. Analyses were based on 410,597 nulliparous women.

(40 patients). The incidence of complications in the SLIT group was lower compared with the control groups as well as the general population. The study suggested that SLIT appears to be safe even when it is initiated for the first time in pregnancy.

Strengths of the current study include the population-based design and large sample size, which practically encompassed all pregnancies in Sweden between 2005 and 2014. Specifically, through nationwide health care registers, we had access to data on nearly one million pregnancies and deliveries and were able to examine the risk for congenital malformations and adverse pregnancy outcomes in virtually all women with records of AIT in pregnancy, which minimized selection bias and contributed to the generalizability of study findings. Misclassification of gestational age, and subsequently preterm birth, SGA, and LGA in the MBR is implausible because since 1990, practically all

pregnant women in Sweden have undergone second-trimester ultrasound.²²

Nulliparity has been linked to spontaneous preterm birth,²³ low birth weight, and SGA birth.²⁴ Restricting the cohort to nulliparous women resulted in similar risk estimates (Table V). Considering that indications of AIT might have changed over time, we performed a separate analysis for the latest calendar period of birth, 2012 to 2014, with equivalent ORs (Table VI).

In the multivariate analyses, we adjusted for a broad range of risk factors, yet the risk for residual confounding was always an issue. We were unable to control for the use of conventional prescription or over-the-counter drugs during pregnancy. However, medications commonly used to treat asthma and allergic rhinitis have not been found to influence pregnancy outcomes.²⁵ Another limitation of this study is that fetal death up to gestational week 22, or until June 2008, stillbirths occurring before gestational week 28 were not reported in the MBR. Hence, we

TABLE VI. Calendar period 2012 to 2014: crude and adjusted odds ratios (ORs) for adverse pregnancy outcomes in pregnancies exposed to allergen-specific immunotherapy (subcutaneous or sublingual)

Adverse pregnancy outcomes	Calendar period 2012 to 2014 (crude OR; 95% CI) (n = 325,121)	Calendar period 2012 to 2014 (adjusted OR; 95% CI) (n = 325,121)
Caesarean delivery	0.76; 0.58-1.00	0.91; 0.69-1.20
Elective	0.82; 0.57-1.18	0.90; 0.62-1.31
Emergency	0.74; 0.52-1.07	0.93; 0.64-1.34
Preterm birth (<37 wk)	0.63; 0.41-0.97	0.71; 0.46-1.10
Congenital malformations	1.02; 0.57-1.81	1.08; 0.60-1.92
Stillbirth	0.35; 0.11-1.10	0.36; 0.12-1.13
Fetal growth		
Small for gestational age	0.80; 0.56-1.13	0.78; 0.55-1.12
Large for gestational age	1.12; 0.76-1.65	1.13; 0.76-1.67
Low Apgar score (<7) at 5 min	0.53; 0.25-1.13	0.61; 0.29-1.30

Crude and adjusted ORs were adjusted for infant sex, maternal age at delivery, maternal country of birth, living with partner, education, parity, body mass index, early pregnancy smoking, and maternal asthma or pulmonary disease. Analyses were based on 325,121 pregnancies with a delivery date in 2012 to 2014. Statistically significant findings are presented in bold italics.

were unable to rule out early fetal loss or early therapeutic pregnancy termination due to congenital malformations. This study was restricted to exploring the overall risk for congenital malformations; thus, data on specific anomalies are not reported. We deemed that the opposite approach might have resulted in wider CIs and a loss of statistical significance or even in reporting false-positive associations in the context of multiple comparisons.

We defined exposure, AIT in pregnancy, based on data from national registers. As far as we know, medical procedure codes for SCIT in the NPR or the Anatomical Therapeutic Chemical code for grass pollen SLIT in the PDR have not been validated. Thus, we cannot rule out that some pregnancies may have been misclassified with regard to exposure. Although it would be challenging to assess the underreporting rate in the NPR accurately, the quality of outpatient data in the register has generally improved through the past 2 decades. Overall, the quality of the PDR is good. The risk for measurement errors should not be an issue because data collection is practically automated and based on administrative systems, whereas information bias is minimized because the PDR warrants coverage of all Swedish residents from birth to death.¹⁸ Considering that starting AIT in pregnant patients remains contraindicated, we performed separate analyses in women with records of AIT first appearing during pregnancy. We found a lower risk for congenital malformations, preterm birth, and low Apgar score (less than 7) at 5 minutes in this subgroup although risk estimates for the other pregnancy outcomes did not differ (Table E2). Although it is beyond the scope of this report, we hypothesize that these observed inverse associations may exist because clinicians tend to initiate AIT in particularly healthy pregnant women without other risk factors or comorbidities.

Systemic allergic reactions including anaphylaxis are significant risk factors in pregnancy.²⁶ Owing to insufficient data and the existing, albeit rare risk for anaphylaxis as a complication of AIT, current guidelines still do not encourage the initiation of

AIT in pregnant women.²⁷ However, if effective and well-tolerated, AIT maintenance therapy in pregnancy may be continued.^{27,28} Regrettably, information on epinephrine use to treat systemic allergic reactions complicating AIT was unavailable in the current pregnancy cohort. Thus, it was impossible to perform separate analyses and study adverse pregnancy outcomes in this specific subgroup.

Regarding Hymenoptera allergy, there is a considerable risk for stinging anaphylaxis during pregnancy when untreated. On the other hand, venom immunotherapy (VIT) per se is a risk factor for anaphylaxis, especially during the induction phase. In our study, among pregnant patients within the SCIT-treated group, some women might have been exposed to VIT. However, because the underlying indications for AIT (eg, allergy to Hymenoptera, pollen, furred pets, or house dust mite) are not recorded in the PDR, we have been unable to perform additional analyses and evaluate adverse pregnancy outcomes for the subgroup of VIT-treated pregnant women. Overall, whether to initiate or maintain VIT in pregnancy should be an individually based decision, and the benefit–risk ratio has to be assessed and discussed with the pregnant patient.²⁶

In general, immune intervention in terms of AIT for the treatment pediatric asthma and allergic rhinitis reduces long-term symptoms and asthma controller medication use.²⁹ Although there has been increasing interest in assessing the allergic response of the offspring in pregnancies exposed to AIT (eg, Oykhman et al³⁰ suggested that neither SCIT nor SLIT altered the risk for developing atopic disease in offspring when it was administered during pregnancy), there are still limited data in this research field. The current study was designed to examine the safety of AIT in pregnancy, especially congenital malformations. Although we found no association with adverse pregnancy outcomes, more studies are needed on the immune response of offspring when mothers are exposed to AIT.

We found no elevated risk for congenital malformations or other adverse pregnancy outcomes in women who received AIT in pregnancy. Despite its limitations, our study is likely to help both physicians and pregnant women make informed decisions about AIT treatment during pregnancy.

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TABLE E1. Crude and adjusted odds ratios (ORs) for adverse pregnancy outcomes in Swedish-born women exposed to allergen-specific immunotherapy (subcutaneous or sublingual) in pregnancy in 2005 to 2014

Adverse pregnancy outcomes	Swedish-born women (crude OR; 95% CI) (n = 706,498)	Swedish-born women (adjusted OR; 95% CI) (n = 706,498)
Caesarean delivery	0.86; 0.70-1.04	0.95; 0.78-1.16
Elective	1.01; 0.77-1.34	1.04; 0.79-1.38
Emergency	0.75; 0.59-0.97	0.88; 0.68-1.13
Preterm birth (<37 wk)	0.98; 0.69-1.40	1.04; 0.73-1.49
Congenital malformations	0.84; 0.58-1.21	0.86; 0.60-1.25
Stillbirth	0.63; 0.20-1.97	0.67; 0.21-2.08
Fetal growth		
Small for gestational age	0.87; 0.67-1.13	0.94; 0.72-1.22
Large for gestational age	1.05; 0.82-1.36	0.95; 0.74-1.23
Low Apgar score (<7) at 5 min	0.91; 0.45-1.83	1.01; 0.50-2.03

Crude and adjusted ORs were adjusted for infant sex, calendar period of birth, maternal age at delivery, living with partner, education, parity, body mass index, early pregnancy smoking, and maternal asthma or pulmonary disease. Analyses were based on 706,498 Swedish-born pregnant women.

Statistically significant findings are presented in bold italics.

TABLE E2. Crude and adjusted odds ratios (ORs) for adverse pregnancy outcomes in women with records of subcutaneous or sublingual allergen-specific immunotherapy (AIT) first appearing during pregnancy in 2005 to 2014

Adverse pregnancy outcomes	AIT initiated during pregnancy (crude OR; 95% CI)	AIT initiated in pregnancy (adjusted OR; 95% CI)
Caesarean delivery	0.73; 0.50-1.05	0.78; 0.54-1.14
Elective	0.72; 0.45-1.16	0.72; 0.45-1.17
Emergency	0.79; 0.48-1.30	0.89; 0.53-1.48
Preterm birth (<37 wk)	0.51; 0.30-0.86	0.53; 0.31-0.91
Congenital malformations	0.52; 0.29-0.93	0.53; 0.29-0.94
Fetal growth		
Small for gestational age	0.66; 0.42-1.04	0.67; 0.43-1.06
Large for gestational age	0.80; 0.50-1.28	0.73; 0.46-1.18
Low Apgar score (<7) at 5 min	0.27; 0.13-0.57	0.28; 0.13-0.60

Crude and adjusted ORs were adjusted for infant sex, calendar period of birth, maternal age at delivery, living with partner, education, parity, body mass index, early pregnancy smoking, and maternal asthma or pulmonary disease. Analyses were based on 165 women with records of AIT first appearing during pregnancy. Stillbirth was observed in none of these pregnancies. Thus, we did not calculate ORs for this pregnancy outcome.

Statistically significant findings are presented in bold italics.

Major malformations				
#	Organ System	ICD-10 codes	Comment	Excluded ICD10 codes for minor defects
1	Nervous System	Q00-Q07		Q0461, Q0782
2	Eye	Q100, Q104, Q106-Q109, Q11-Q12, Q130-Q134, Q136-Q139, Q14-Q15		
3	Ear, Face and Neck	Q16, Q176-Q178, Q183, Q188		Q1880
4	Congenital Heart Defects	Q20-Q25, Q260, Q262-Q269	Q250 and Q256 were not included if GA<37w	Q211C/Q2111, Q2541
5	Respiratory System	Q300, Q321-Q329, Q330, Q332-Q335, Q337-Q339, Q34		
6	Orofacial Clefts	Q35-Q37		
7	Digestive System	Q380, Q383-Q389, Q39, Q402-Q409, Q41-Q42, Q431-Q439, Q44-Q45, Q790	Q385A was not included	Q4320-Q4021, Q4381-Q4382
8	Abdominal Wall Defects	Q792-Q793, Q795		
9	Urinary System	Q60, Q611-Q619, Q620-Q626, Q628-Q629, Q630-Q632, Q634-Q639, Q64, Q794		
10	Genital Organs	Q50-Q51, Q520-Q522, Q524, Q526, Q528-Q529, Q54-Q56		Q552f/Q5520, Q5521
11	Limb	Q660-Q661, Q679, Q681-Q682, Q686-Q689, Q70-Q74		Q6810, Q682A/Q6821, Q740G/Q7400
12	Other	Q750, Q77, Q782-Q788, Q80-Q81, Q820-Q824, Q826-Q829, Q860, Q890, Q893-Q894		Q7980, Q7982, Q828A/Q8280
X	Teratogenic/genetic syndromes, microdeletions and chromosomal abnormalities	D821, P350-P352, P371, Q619, Q751, Q754, Q771-Q772, Q780, Q796, Q85, Q861-Q869, Q87, Q90-Q92, Q930-Q939, Q95-Q99	All infants with any of these ICD codes were excluded	Q447B/Q4471, Q7484

FIGURE E1. International Classification of Diseases, 10th Revision (ICD10) codes for major congenital malformations.