

A population analysis of prescriptions for asthma medications during pregnancy

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Background: It is important to control asthma during pregnancy. However, some studies indicate that women stop or change their asthma medications when they become pregnant. **Objective:** We used a population database to analyze changes in prescriptions for asthma medications to patients before, during, and after pregnancy.

Methods: We collected information from a pregnancy database that is part of the population-based pharmacy prescription InterAction Database from the northern Netherlands. Our study cohort comprised 25,709 pregnancies for which prescription data were available. We collected data over a study period of 1 year before pregnancy until 6 months after birth and analyzed data from pregnant women who received at least 1 prescription for asthma medication during the study period ($n = 2072$), identifying all prescriptions for asthma medication and oral corticosteroids.

Results: Prescriptions for asthma medications did not change during pregnancies from 1994-2003. However, during the 2004-2009 period, there was a significant decrease ($P = .017$) in prescriptions for asthma medications during the first months of pregnancy compared with the months before pregnancy, especially prescriptions of long-acting bronchodilators.

Although most asthma prescriptions continued throughout pregnancy, prescriptions for controller therapies were reduced by 30% during the first months of pregnancy.

Conclusions: Many women stop or reduce their use of asthma medications when they become pregnant. Strategies to safely control asthma during pregnancy are needed. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Drug use, asthma medication, asthma guidelines, pregnancy

Drug use during pregnancy cannot always be avoided, especially for women with chronic conditions. During the last decades, the prevalence of asthma has increased worldwide, with an estimated 3% to 12% of pregnant women having asthma.^{1,2} Poor asthma control is associated with maternal and neonatal complications, such as preeclampsia, preterm delivery,

Abbreviations used

IADB: InterAction Database

NHG: Dutch College of General Practitioners

and low birth weight, and therefore adequate treatment is important.^{1,3,4} However, the safety of many asthma drugs for use during pregnancy has not been determined.⁵

The Netherlands has no official published guidelines about the use of asthma medication during pregnancy.⁶ The Dutch College of General Practitioners (NHG) has stated that pregnant women can continue taking short-term β_2 -adrenergic receptor agonists and the inhaled corticosteroids budesonide and beclomethasone. Less is known about the effects of fluticasone during pregnancy, but continuation seems safe. Little is known about the effects of long-acting β_2 -agonists, anticholinergic agent, or leukotriene modifiers, and therefore NHG guidelines advise against the use of these medications during pregnancy. In cases of serious exacerbation, the risks of hypoxemia outweigh those of systemic corticosteroids.⁷

The Global Initiative for Asthma, which was formed in 1993, works with health care professionals and public health officials to reduce asthma prevalence, morbidity, and mortality.⁸ Their reports form the basis for many national guidelines.⁹ In 2010, they published a report stating "Pregnant women with asthma should be advised that greater risk to their baby lies with poorly controlled asthma and the safety of most modern asthma treatments should be stressed."⁹ The US National Asthma Education and Prevention Program stated that maintaining adequate control of asthma during pregnancy is important for the health and well-being of mothers and babies. The inadequate control of asthma is a greater risk to the fetus than asthma medication.⁴ Nonetheless, many women are concerned about the risks of asthma medications during pregnancy and consider discontinuation.¹⁰ Reduced use of asthma medication during the first trimester of pregnancy was reported in some studies.^{11,12}

To investigate the continued use of different asthma medications throughout pregnancy, we tracked numbers of asthma prescriptions using a Netherlands database. We compared numbers of prescriptions for asthma medication written up to 2003 with those from 2004 to 2009 to identify changes associated with the increased emphasis on the importance of asthma control during pregnancy.

METHODS

Database

This study was performed by using a pregnancy database that is part of the population-based pharmacy prescription InterAction Database (IADB). The IADB contains data on prescriptions filled at 55 pharmacies in the northern Netherlands, covering a population of approximately 500,000 subjects from

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TABLE I. Number of pregnancies with at least 1 prescription of a drug or group during each time period

	Months before pregnancy				Months during pregnancy*			Months after pregnancy	
	12-10	9-7	6-4	3-0	0-3	3-6	6-9	0-3	3-6
Short-acting bronchodilators†	497	477	485	468	463	470	459	402	428
Salbutamol	434	415	424	419	418	422	420	365	392
Terbutaline	41	50	44	40	35	31	27	26	30
Ipratropium	31	18	25	16	24	32	28	17	11
Ephedrine	1	0	0	0	0	0	0	0	0
Salbutamol, oral	0	0	0	0	1	0	1	0	0
Terbutaline, oral	1	3	3	0	1	0	0	0	0
Salbutamol + ipratropium	1	0	0	2	1	1	0	0	0
Inhaled corticosteroids†	345	355	328	343	350	369	341	302	330
Beclomethasone	160	157	145	146	229	248	248	169	159
Budesonide	107	115	108	104	81	73	65	79	97
Fluticasone	80	86	78	95	55	53	32	57	77
Ciclesonide	0	0	1	0	0	0	0	0	1
Long-acting bronchodilators†	62	59	72	56	41	26	29	32	53
Salmeterol	29	27	31	27	17	8	10	12	25
Formoterol	27	27	35	24	21	15	14	15	23
Tiotropium	4	6	5	3	1	1	1	2	3
Fenoterol	2	1	3	2	3	3	4	3	4
Fenoterol + ipratropium	1	0	1	0	1	1	1	1	0
Combination preparations†	80	85	95	106	54	42	44	79	102
Fluticasone + salmeterol	58	59	64	77	35	25	29	53	68
Beclomethasone/budesonide + formoterol	22	26	32	30	19	17	15	26	34
Other medications†	31	26	28	23	16	17	18	17	15
Cromoglycic acid	18	15	17	11	11	13	13	11	9
Montelukast	12	9	9	10	4	2	2	6	5
Theophylline	1	2	2	2	1	2	3	1	1

Values are based on data from 25,709 pregnancies in the IADB.

*Months 1 to 3 of pregnancy refer to the first trimester, months 4 to 6 refer to the second trimester, and months 7 to 9 refer to the third trimester of pregnancy.

†Because there can be more than 1 prescription for a drug in each group, numbers do not always add up.

1994 to 2009. Because of the high level of commitment of patients to their pharmacies, the IADB contains an almost-complete medication history for each subject registered. The database contains information on all prescriptions filled, except medications prescribed during hospitalization. Information about over-the-counter drugs is not available. Each prescription contains the code of the drug according to the Anatomical Therapeutic Chemical classification,¹³ along with the date of dispensation, amount dispensed, dose regimen, and prescriber. Each patient has a unique anonymous identification number, and date of birth and sex are listed.

Pregnancies in the IADB can be identified by connecting every child listed with a 15 to 50-year-old female subject with the same address code, providing there are no other women in this age range with the same address code. Using this method, mothers of 64.9% of the children listed in the IADB could be identified. Validation of this method is described elsewhere.¹⁴ The pregnancy period was estimated by subtracting 273 days (3 trimesters of 91 days) from each child's date of birth.

Study population

We analyzed data from pregnancies for which complete data were available from 1 year before the theoretic date of conception until 6 months after birth and for which the mother had at least 1 prescription of asthma medication during this period. For these pregnancies, we identified all prescriptions of asthma medication (R03) and oral corticosteroids (H02).

The prescription rate was defined as the percentage of all pregnancies with at least 1 prescription of a drug or drug group in a defined period. Differences were tested with R version 2.10.1 software by using Pearson χ^2 analysis with Yates continuity correction.

We defined chronic use of a drug or a drug group as at least 3 prescriptions for that drug or drug group in the year before pregnancy. We classified asthma drugs into the following categories: short-acting bronchodilators, inhaled

corticosteroids, long-acting bronchodilators, combination preparations of an inhaled corticosteroid and a long-acting bronchodilator, and other medications (Table I). All but the short-acting bronchodilators are considered controller medications. For all chronic users of a drug or drug group in the year before pregnancy, it was determined whether they continued taking the same drug or a drug from this group, switched to another asthma medication, or stopped taking asthma medication in the first trimester of pregnancy.

We used chronic use of asthma controller therapy (≥ 3 preparations of controller medication in the year before pregnancy) as a proxy for actual asthma.

RESULTS

The study cohort comprised 25,709 pregnancies for which prescription data were available during the study period (from 1 year before until 6 months after pregnancy). Of these pregnancies, 2072 (8.1%) in 1695 women involved at least 1 prescription of asthma medication during the study period, including 55 twin pregnancies and 1 triplet pregnancy. The women were a mean age of 30.0 years (range, 15-48 years) when they gave birth after the 2072 pregnancies. In 52 (2.5%) of the pregnancies, the woman was 40 years or older. Table I shows the asthma medication (Anatomical Therapeutic Chemical code starting with R03) that was prescribed to the study population during the study period.

Fig 1 shows classifications of the prescription rates. Of the 2072 pregnancies in which asthma medication was prescribed during the study period, 703 (33.9%) included prescriptions for short-acting medication only, 401 (19.4%) included at least

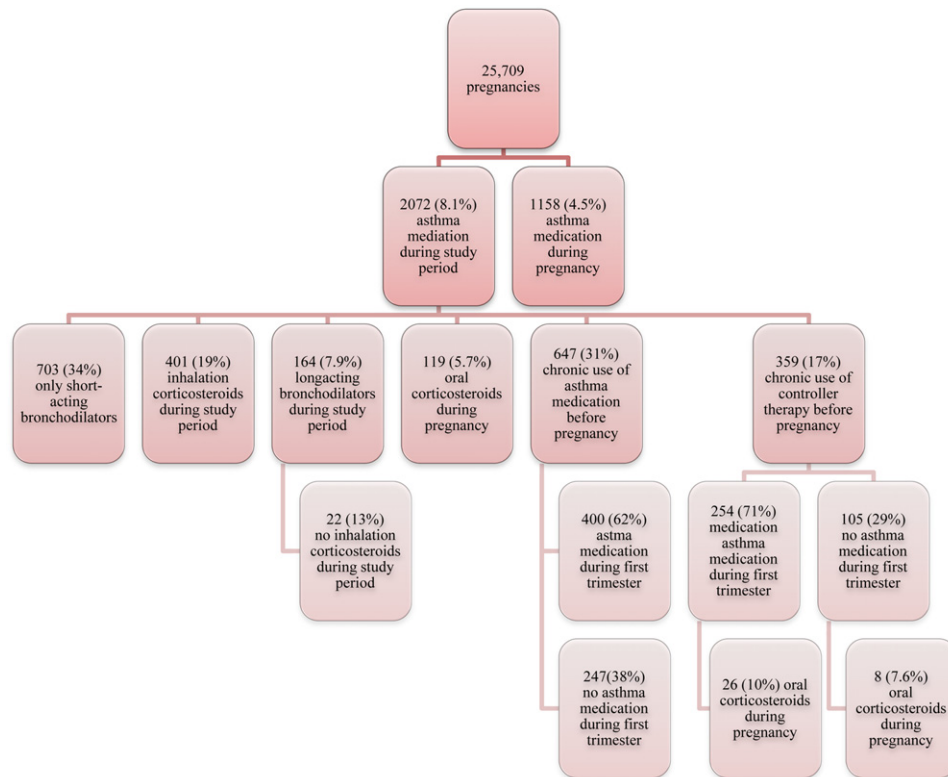


FIG 1. Classification of asthma drug use during pregnancy. Of the 2,072 pregnancies in which asthma medication was prescribed during the study period, 703 (33.9%) included prescriptions for short-acting medication only, 401 (19.4%) included at least 1 prescription of oral corticosteroids, and 119 (5.7%) included at least 1 prescription for an oral corticosteroid during pregnancy, indicating an exacerbation. Long-acting bronchodilators were prescribed during 164 (7.9%) pregnancies; 22 (13.4%) of these included no additional inhaled corticosteroids. Asthma drugs were used during the months of actual pregnancy (rather than the entire study period) in 1,158 pregnancies.

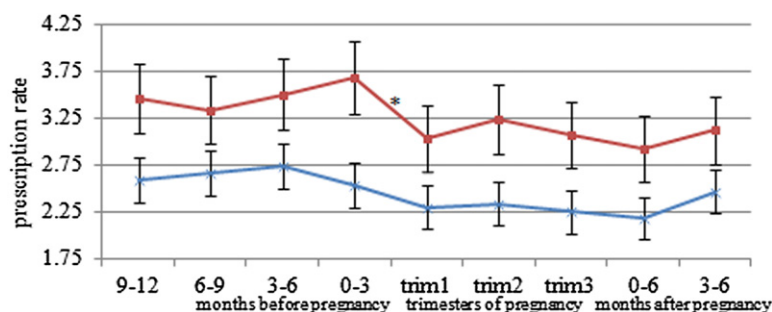


FIG 2. Prescription rate during the study period: percentage of all pregnancies with at least 1 asthma drug prescription during different stages of the study period through the end of 2003 (blue line) and from 2004 to 2009 (red line). The asterisk indicates a significant decrease in prescription rate.

1 prescription of oral corticosteroids, and 119 (5.7%) included at least 1 prescription for an oral corticosteroid during pregnancy, indicating an exacerbation. Long-acting bronchodilators were prescribed during 164 (7.9%) pregnancies; 22 (13.4%) of these included no additional inhaled corticosteroids.

Fig 2 compares the prescription rate through the end of 2003 with the rate from 2004 to 2009. From 2004 to 2009, more asthma medications were prescribed than in the period through 2003 ($P < .001$). During the 2004–2009 period, there was a significant decrease ($P = .017$) in prescriptions for asthma medications in the first trimester of pregnancy compared with the

3 months before pregnancy. In the period through 2003, there was no significant decrease in asthma medication use during the first trimester.

Fig 3 compares the prescription rates for the main groups of asthma medications during different stages of the study period until 2003 and from 2004 to 2009. In the period until 2003 (Fig 3, A), there was fluctuation in the prescription rates of the different groups of asthma medications over the study period, but no changes were statistically significant. From 2004 to 2009 (Fig 3, B), there was a significant decrease in prescription rates of long-acting bronchodilators and combination preparations

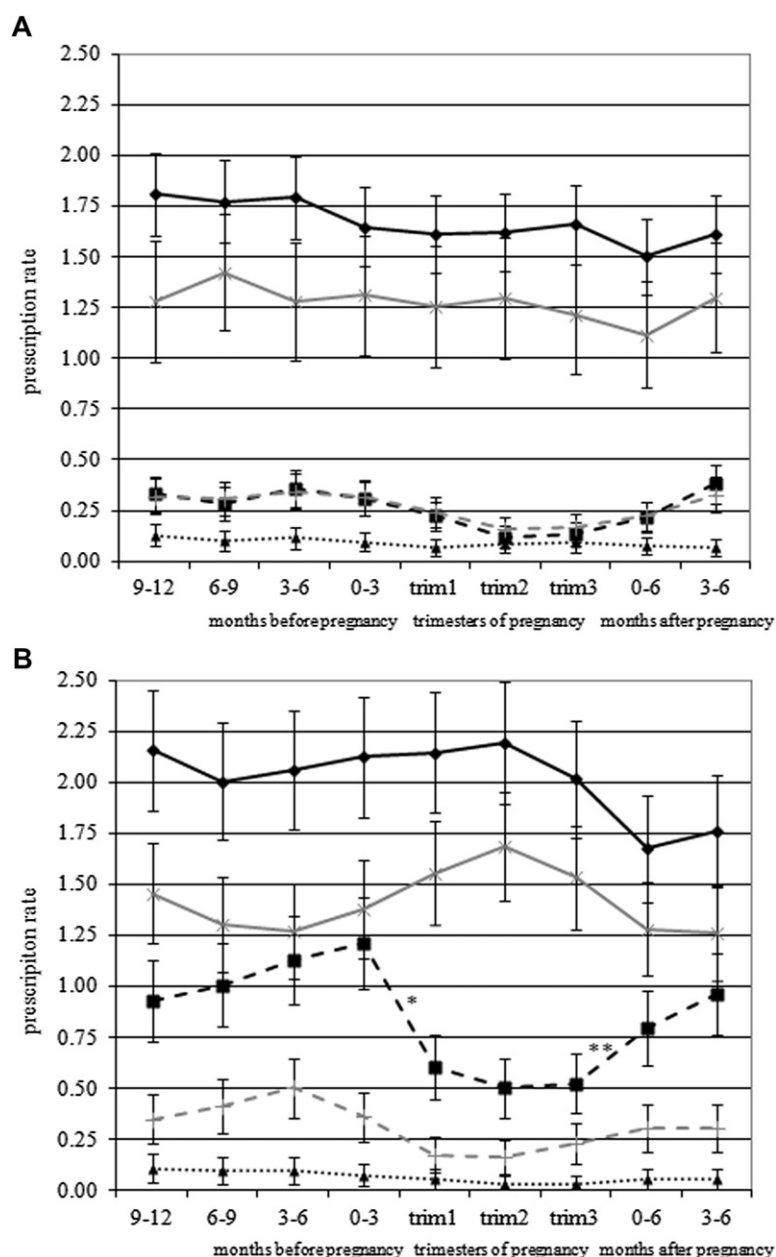


FIG 3. A, Prescription rate of the main groups of asthma medications until 2003. A comparison of the prescription rates for the main groups of asthma medications during different stages of the study period until 2003 was performed. There was fluctuation in the prescription rates of the different groups of asthma medications over the study period, but no changes were statistically significant. *Black solid line*, Short-acting bronchodilators; *gray solid line*, inhaled corticosteroids; *black dashed line*, long-acting bronchodilators and combinations; *gray dashed line*, oral corticosteroids; *black dotted line*, other asthma medications. **B,** Prescription rate of the main groups of asthma medications from 2004 to 2009. A comparison of the prescription rates for the main groups of asthma medications during different stages of the study period from 2004 to 2009 was performed. *There was a significant decrease in prescription rates of long-acting bronchodilators and combination preparations from the months before pregnancy to the first trimester of pregnancy ($P < .001$). **There was then a significant increase in prescription rates of these drugs from the last trimester of pregnancy to the first months after pregnancy ($P = .029$). *Black solid line*, Short-acting bronchodilators; *gray solid line*, inhaled corticosteroids; *black dashed line*, long-acting bronchodilators and combinations; *gray dashed line*, oral corticosteroids; *black dotted line*, other asthma medications.

from the months before pregnancy to the first months of pregnancy ($P < .001$). There was then a significant increase in prescription rates of these drugs from the last months of pregnancy to the first months after pregnancy ($P = .029$).

The decrease in prescription rates of long-acting bronchodilators during the first few months of pregnancy from 2004 to 2009 was observed for groups of women younger and older than 31 years (data not shown). However, among women 31 years and

TABLE II. Change in prescriptions during the first trimester of pregnancy versus the year before

	Any asthma medication*	Short-acting bronchodilators	Inhalation corticosteroids	Long-acting bronchodilators	Combination preparations	Other asthma medication (%)
Chronic users of drugs in the year before pregnancy	647	319	231	52	74	24
Patients who continued		203 (63.6%)	122 (52.8%)	22 (42.3%)	32 (43.2%)	12 (50.0%)
Change to:						
Beclomethasone				12 (23.1%)	11 (14.9%)	2 (8.3%)
Budesonide				3 (5.8%)	2 (2.7%)	0
Short-acting bronchodilators			2 (0.9%)	6 (11.5%)	8 (10.8%)	0
Patients who stopped taking the drug	247 (38.2%)	93 (29.2%)	61 (26.4%)	8 (15.4%)	18 (24.3%)	5 (20.8%)

*Anatomical Therapeutic Chemical code starting with R03.

TABLE III. Asthma severity and strategy for treatment^{4,7}

Asthma severity	Treatment step	Symptoms	Preferred treatment
Intermittent	Step 1	Twice a week or less	Short-acting bronchodilator, as needed
Mild persistent	Step 2	More than twice a week	Low dose of inhaled corticosteroids to be increased to a medium dose if symptoms are not controlled sufficiently; short-acting bronchodilator, as needed
Moderate Persistent	Step 3	Symptoms not sufficiently under control with step 2 medication	Medium dose of inhaled corticosteroids and a long-acting inhaled bronchodilator; short-acting bronchodilator, as needed
Severe persistent	Step 4	Symptoms not sufficiently under control with step 3 medication	High dose of inhaled corticosteroids and a long-acting inhaled bronchodilator and corticosteroid tablets, if needed; short-acting bronchodilator, as needed

older, the decrease was compensated by an increased prescription rate of short-acting bronchodilators and inhaled corticosteroids (data not shown). The prescription of inhaled corticosteroids tends to increase during pregnancy, but this observed increase was not statistically significant.

Table II shows the change in prescriptions during the first trimester of pregnancy among women who consistently used asthma drugs (≥ 3 prescriptions) of each category in the year before pregnancy. Most asthma prescriptions continued throughout pregnancy. When regular asthma medication was changed to an inhaled corticosteroid during pregnancy, it was usually switched to beclomethasone; there were only a few changes to budesonide. Within the class of inhaled corticosteroids, there was a switch to beclomethasone in the first trimester of pregnancy for 16 (25.8%) of 62 pregnancies with at least 3 prescriptions of fluticasone in the year before pregnancy and none to budesonide (not shown).

Of 647 pregnancies with at least 3 prescriptions of asthma medication during the year before pregnancy, 247 (38.2%) did not have a prescription for any asthma medication during the first trimester of pregnancy. Of all pregnancies defined as having asthma present (≥ 3 prescriptions for a controller medication in the year before pregnancy, $n = 359$), 105 (29.2%) did not include a prescription for any asthma medication during the first months of pregnancy (Fig 1). There was no statistical difference in numbers of pregnancies including at least 1 prescription for oral corticosteroids during pregnancy between pregnancies with or without prescriptions of asthma medication during the first trimester of pregnancy ($P = .44$).

DISCUSSION

This study shows a significant increase in prescriptions for asthma medications among pregnant women in the period from

2004 to 2009 compared with the period before 2004. The increase was greatest for long-acting bronchodilators and combination preparations (Fig 3). The increase in prescriptions of asthma medications was likely due to the increasing prevalence and awareness of asthma.^{1,2} Long-acting bronchodilators and combination preparations are relatively new agents that have been increasingly prescribed since 2000 as add-on therapies to inhaled corticosteroids.

Despite their understanding of the importance of adequate asthma control, many women stop their controller therapy when they become pregnant. We observed a significant decrease in prescriptions of asthma medications during the first trimester of pregnancy in the period from 2004 until 2009, especially for long-acting bronchodilators, either as separate preparations or in combination with inhaled corticosteroids. This group contains relatively new agents, and their safety during pregnancy has not been established.

The NHG standard advises against use of this medication during pregnancy,⁷ but the Global Initiative for Asthma guidelines and the National Asthma Education and Prevention Program stress the importance of controlling asthma symptoms, even when the safety of medications has not been proved.^{4,9} A long-acting bronchodilator is usually added to therapy with an inhaled corticosteroid when a medium dose of inhaled corticosteroids does not achieve adequate control (Table III).^{4,7} Therefore long-acting bronchodilators are usually prescribed for patients with more severe asthma, and discontinuation could lead to severe symptoms of respiratory distress.

Almost 30% of pregnancies in which controller therapy for asthma was consistently used in the year before pregnancy did not include a prescription for any asthma medication during the first trimester of pregnancy. This might be partly due to the fluctuating course of asthma. Blais et al¹¹ and Enriquez et al¹²

reported decreased use of short-acting bronchodilators and inhaled corticosteroids in the first trimester of pregnancy based on data until 2000 and 2001, respectively. However, long-acting bronchodilators were not yet commonly used during these time periods.

In a study of drug prescription patterns in The Netherlands, Bakker et al¹⁵ found that most drugs for chronic conditions were prescribed less during pregnancy. In the months after pregnancy, prescription rates increased, although not to prepregnancy levels, most likely because of breast-feeding. Alternatively, the prescription rate of asthma medication decreased slightly in the months after pregnancy, as we observed (Fig 2).¹⁵ Engeland and Bramness¹⁶ also showed a decrease in the prescription of asthma medication during the first trimester of pregnancy and another in the 3 months after pregnancy in Norway, as did Malm and Martikainen¹⁷ in a study of prescription drug use during pregnancy and lactation in Finland.

Of the women who no longer received prescriptions for long-acting bronchodilators or combination preparations when they became pregnant, more than 10% who did not have a prescription for a short-acting bronchodilator before pregnancy had such a prescription during pregnancy, indicating a worsening of symptoms and less asthma control. Women who stopped controller therapy when they became pregnant appeared prone to exacerbations.

Postpartum, asthma severity usually returns to the prepregnancy state within 3 months,¹⁸ and therefore an increase to prepregnancy prescription levels would be expected, with a possible delay because of women's reluctance to use medications during breast-feeding. We observed prescriptions of asthma medication to return to prepregnancy levels within 6 months after birth (Fig 2).

Inhaled corticosteroids are the drugs of choice to treat persistent asthma (Table III). Women with asthma who, on becoming pregnant, stopped their prescription for their usual controller medication and received a prescription for another drug, were most likely to switch to beclomethasone; only a few changed to budesonide (both are inhaled corticosteroids, Table II). Guidelines often state that budesonide is the first choice of inhaled corticosteroid for pregnant women because this drug has the most data available.^{4,9} In The Netherlands beclomethasone is the inhaled corticosteroid of first choice for pregnant patients.¹⁹

Long-acting bronchodilators are only to be used for the treatment of asthma when they are combined with an inhaled corticosteroid because the long-acting bronchodilators do not affect airway inflammation. This drug is added to therapy when asthma symptoms are not controlled by inhaled corticosteroids.^{7,9} However, in our study population 14.4% of all pregnancies including at least 1 prescription for a long-acting bronchodilator included no prescriptions for inhaled corticosteroids during the study period (1 year before to 6 months after pregnancy). This is not a correct treatment strategy. If health care practitioners do not prescribe inhaled corticosteroids, there are effective alternatives, including monotherapy with leukotriene modifiers or theophylline.^{4,7,9}

For our study population, complete data were available on all asthma medications prescribed in the period from 1 year before until 6 months after pregnancy. We compared prescriptions during the period before pregnancy with those during pregnancy, and therefore each woman served as her own control subject.

However, this study has certain limitations. Because the IADB only contains prescription data, it is not known whether the

medication was actually taken. This could lead to an overestimation of drug use. Also, asthma medication is often taken as needed and used for a long period after it was prescribed, which could result in underestimation of drug use. Furthermore, the IADB has no information about medications prescribed during hospitalization, which could lead to an underestimation of exacerbations and medications prescribed.

We do not have information about the indication for each prescription. This could lead to overestimations of asthma cases and exacerbations. Oral corticosteroids, for example, can be prescribed for a number of indications other than asthma. Also, 2.5% of the pregnancies in the study were in women 40 years or older, and therefore some cases that we considered to be asthma might actually have been chronic obstructive pulmonary disease.

Antihistamines are often prescribed to patients with asthma who also have allergic rhinitis.²⁰ Antihistamines are prescribed for many allergic symptoms, as well as for nausea and vomiting, which is a common problem during the first months of pregnancy. Because we did not have information about indications, we did not analyze data on prescriptions for antihistamines.

We used 273 days, the mean length of gestation, to calculate dates of conception and months after birth. Some periods might therefore have been misclassified, and actual differences between trimesters might have been underestimated. Furthermore, the IADB only includes information about live births; data on abortions, miscarriages, and stillbirths are not included. A pregnancy is only identified when the child is dispensed a prescribed drug and can be coupled to a mother.

Because we have had no contact with the women included in the study or their physicians, it is unclear whether decisions to discontinue or change prescriptions were made by the pregnant women or their physicians. Even pharmacists can be involved in changing prescriptions.

Our study covers a long period (from 1994 until 2009) during which the importance of adequate control of asthma during pregnancy has gained attention. We did not see an improvement in the continuation of asthma prescriptions throughout pregnancy when we compared the period up to 2003 with the 2004-2009 period.

A study of perceptions of asthma treatment during pregnancy by Chambers¹⁰ found that only 19% of participating women had discussed with their physician the need to continue taking their asthma medication if they were to become pregnant; 39% of women who became pregnant reduced their asthma medication, and a third of these did so without discussing it with their physicians. However, many women would change their minds if given accurate information about the risks of their medications or if continuation was recommended by their caregivers.¹⁰ Patients and even doctors tend to overestimate the risks of most medication during pregnancy.²¹ Therefore for women to make the right decision about their asthma medication before they become pregnant, they should be thoroughly informed about its risks and benefits.

A recent study by Lim et al²² found that 26% of general practitioners who responded to a survey would stop or reduce the dosage of controller medication when a patient became pregnant, even though her asthma symptoms were well controlled. Physicians should keep up to date on the latest research findings about continuation of asthma medications during pregnancy and explain these to patients who might become pregnant.

In conclusion, almost 30% of women with asthma stop their controller therapy when they become pregnant. This can lead to poor control of asthma and increased risk of exacerbations, along with risk of maternal and neonatal complications. There is room for improvement in treating asthma in pregnant women, which could lead to better health and care for mothers and children.

Key messages

- Many women with asthma stop controller therapy when they become pregnant. This can lead to poor control of asthma symptoms and increased risk for exacerbations, along with maternal and neonatal complications.
- Physicians should keep up to date with research findings on the safety of asthma medications during pregnancy and explain these to patients who might become pregnant.

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