

Effect of pregnancy in asthma on health care use and perinatal outcomes

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Background: It is generally known that pregnancy in asthmatic patients increases the risk of asthma exacerbations and poor perinatal outcomes. However, the effect of pregnancy in asthmatic patients on health care use is not known well. In addition, its effect on perinatal outcomes is still controversial because of study limitations caused by ethical issues. National Health Insurance claim data are an ideal resource for studying real-world health care use patterns of asthma.

Objective: We sought to evaluate the effect of pregnancy on asthma in terms of asthma-related health care use and prescription patterns in concert with the effect of asthma exacerbations on adverse pregnancy outcomes.

Methods: Among all asthmatic patients in the Korean National Health Insurance claim database from January 2009 to December 2013, pregnant women who delivered in 2011 with pre-existing asthma were enrolled. Analyses included asthma-related health care use and prescription patterns compared between pregnant asthmatic women and nonpregnant female asthmatic control subjects, as well as within the pregnant subjects from before pregnancy throughout postpartum periods. In addition, the association between asthma exacerbation during pregnancy and adverse pregnancy outcomes was assessed.

Results: A total of 3,357 pregnant asthmatic patients were compared with 50,355 nonpregnant asthmatic patients, and 10,311 pregnant patients were included to determine the effect of asthma exacerbations on adverse pregnancy outcome in the study. Pregnant asthmatic patients underwent more asthma-related hospitalizations (1.3% vs 0.8%, $P = .005$) but had significantly fewer outpatient visits and prescriptions for most

asthma medications than nonpregnant asthmatic patients. The proportion of patients ever hospitalized gradually increased throughout pregnancy (first trimester, 0.2%; second trimester, 0.5%; and third trimester, 0.7%; $P = .018$). The prevalence of asthma exacerbation during pregnancy was 5.3%, and the patients who had acute exacerbation during pregnancy had significantly higher asthma-related health care use in terms of hospitalization, intensive care unit admission, and emergency department and outpatient visits within 1 year before delivery than those who had not. However, asthma exacerbation during pregnancy was not significantly related to adverse perinatal outcomes, except for cesarean section (27.1% vs 18.9%, $P < .001$). All exacerbations were managed with systemic corticosteroids, and the patients who ever experienced acute exacerbations maintained asthma medications, including inhaled corticosteroid-based inhalers, throughout the pregnancy period.

Conclusion: Pregnancy profoundly affects asthma-related health care use but to a different degree depending on whether the patient experienced an exacerbation. Asthma exacerbation during pregnancy is not associated with adverse pregnancy outcomes while managed appropriately with systemic corticosteroids. However, further studies are needed to clarify the effect of asthma control on perinatal outcome and delivery method. (*J Allergy Clin Immunol* 2015;■■■:■■■-■■■.)

Key words: Asthma, health care, insurance claim review, pregnancy

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Supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (grant nos. H114C1971 and H113C0776).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 15, 2014; revised April 21, 2015; accepted for publication April 22, 2015.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2015.04.043>

Asthma is a common chronic medical condition that represents a significant public health issue and can cause serious complications in pregnancy. The prevalence of asthma among pregnant women varied from 3.7% to 13.9% in several studies conducted with different populations, methodologies, and case definitions¹⁻⁴ and appears to have increased in recent decades.^{1,3,5} Maternal asthma during pregnancy increases the risk of poor perinatal outcomes, including low birth weight, preterm delivery, preeclampsia, and perinatal fetal death.⁶⁻¹³ Moreover, asthma exacerbations during pregnancy have been linked to these outcomes.¹⁴⁻¹⁸ However, these studies have had conflicting results in terms of corticosteroid use, general treatments, and asthma severity. For instance, a recent meta-analysis found that exacerbations of asthma during pregnancy are associated with low birth weight but not preterm delivery or preeclampsia.¹⁹ In reality, it is difficult to overcome such inconsistencies with well-designed clinical studies because trials in pregnant asthmatic patients are considered unethical.

There is extensive evidence for the safety of inhaled corticosteroids (ICSs) as asthma treatment during pregnancy.²⁰⁻²² Nevertheless, the lack of appropriate treatment with ICSs is considered one of the major contributors to exacerbation during

Abbreviations used

ED: Emergency department
 ICD-10: International Classification of Diseases, 10th revision
 ICS: Inhaled corticosteroid
 ICU: Intensive care unit
 LABA: Long-acting β_2 -agonist
 NHI: National Health Insurance
 SABA: Short-acting β_2 -agonist

pregnancy.^{23,24} In fact, many pregnant women with asthma and some physicians remain apprehensive of using asthma medications because of concern for the fetus, increasing the risk of acute asthma exacerbations, which in turn could be associated with poorer perinatal outcomes.

A longitudinal study of patients with asthma during pregnancy has the advantage of being able to assess the relationship between health care use patterns and perinatal outcomes. In this respect insurance claims data are valuable for long-term follow-up of patients' health care use. Korea has a unique National Health Insurance (NHI) system as a single insurer that covers almost the entire population.²⁵ Hence health care use and prescription patterns can be tracked, and longitudinal clinical information can be obtained from the NHI database for almost all asthmatic patients in Korea, making it possible to evaluate real-world practice.²⁶

This study was performed to evaluate asthma prescription patterns and asthma-related health care use before pregnancy, during pregnancy, and after delivery. Furthermore, adverse pregnancy outcomes in patients with acute asthma exacerbations during the pregnancy period were evaluated by using NHI claims data.

METHODS

Study subjects and design

This study was conducted as a retrospective, population-based study to investigate health care use and prescription patterns associated with asthma during pregnancy by using NHI claims data between January 1, 2009, and December 31, 2013. In this study we included all patients who met the following criteria: (1) women aged 18 years or older; (2) women given a diagnosis of asthma as the principle (first listed) or additional 4 diagnostic codes according to the International Classification of Diseases, 10th revision (ICD-10; J45.x-J46.x for the principal and additional diagnoses); and (3) women prescribed asthma-related medication (inhaled, oral, or intravenous) or who underwent asthma-related tests at least once during the 5 years of the study. Asthma-related medications included ICSs, ICSs combined with long-acting β_2 -agonists (LABAs), oral leukotriene antagonists (LTRAs), short-acting β_2 -agonists (SABAs), systemic LABAs, xanthine derivatives, and systemic corticosteroids. Asthma-related tests included spirometry with or without bronchodilator response and the bronchial provocation test.²⁶

Of these patients, pregnant women who had one of the procedure codes related to delivery during 2011 and were given a diagnosis of asthma before their pregnancy period were enrolled in our study (Fig 1 and see Table E1 in this article's Online Repository at www.jacionline.org). The pregnancy period was defined as a duration of 280 days (40 weeks) before the date of delivery, as recorded with the procedure codes in the NHI claims database. Nonpregnant female asthmatic patients were also included as control subjects for comparing their asthma-related health care use and prescription patterns with those of pregnant asthmatic patients after matching of the baseline exacerbation history and age (see Fig E1; detailed descriptions are shown in the Methods section in this article's Online Repository at www.jacionline.org). The

presence of asthma exacerbation was considered when satisfying at least 1 of the following 3 conditions: (1) asthma-related hospitalization; (2) asthma-related emergency department (ED) visit; or (3) asthma-related outpatient visit with systemic corticosteroid prescription.

In addition, for analysis of the association between adverse pregnancy outcomes and exacerbations of asthma during pregnancy, the study subjects were extended to pregnant women who had a delivery procedure code from 2011 to 2013. Adverse pregnancy outcomes were tracked throughout the entire period of pregnancy until 2 months after delivery.

Data source and ethical considerations

The NHI claims data were provided by the Korean Health Insurance Review and Assessment Service, an independent body established to review claims data and assess the quality of health care in Korea. The Health Insurance Review and Assessment Service-run database contains information concerning all submitted claims and prescriptions. This study was approved by the Ethics Committee of the National Evidence-Based Healthcare Collaborating Agency.

Statistical analysis

Nonpregnant female control subjects were selected by using a stratified random sampling method. Each pregnant case was matched to 15 nonpregnant female control subjects based on 2 factors: the presence or absence of asthma exacerbation within 1 year before the analysis period and age by decade (20-29, 30-39, and 40-49 years). The matching ratio was chosen as 15:1 because it was the lowest ratio of control subjects to pregnant cases among the matched pairs in accordance with the presence of asthma exacerbation in each age decade (see Table E2 in this article's Online Repository at www.jacionline.org). Frequencies and percentile distributions were used to describe categorical variables, such as hospitalizations, intensive care unit (ICU) admissions, or ED or outpatient visits and the number of patients prescribed asthma medications at least once. Continuous variables, including hospitalization days and number of health care uses, were presented as means $\pm$ SDs. χ^2 Tests were used to compare categorical variables, and independent Student *t* tests or ANOVA were used to compare continuous variables. Differences were considered significant when the *P* value was less than .05. All analyses were performed with SAS statistical software (version 9.2).

RESULTS

Effect of pregnancy on asthma-related health care use

A total of 3357 pregnant women with asthma over 2010 and 2011 were enrolled in this study. Approximately 1.3% of pregnant asthmatic patients were hospitalized at least once during pregnancy, which was a significantly higher rate than among nonpregnant asthmatic patients after adjusting for age group and asthma exacerbation history in the previous year (1.3% vs 0.8%, *P* = .005). The average number of hospitalizations and length of stay per person among pregnant patients who had ever been hospitalized were 1.33 ± 0.69 times and 10.29 ± 10.51 days, respectively, and there were no significant differences between pregnant and nonpregnant asthmatic patients. None of the pregnant cases were admitted to the ICU, and only 0.4% received treatment in the ED for an asthma exacerbation, with similar results in the nonpregnant control subjects. Meanwhile, pregnant patients were observed to have less frequent outpatient visits related to asthma compared with nonpregnant control subjects (*P* < .001). Prescriptions of almost all asthma medications, including ICS/LABA combinations in a single inhaler, LTRAs, SABAs, systemic LABAs, xanthine derivatives, and systemic

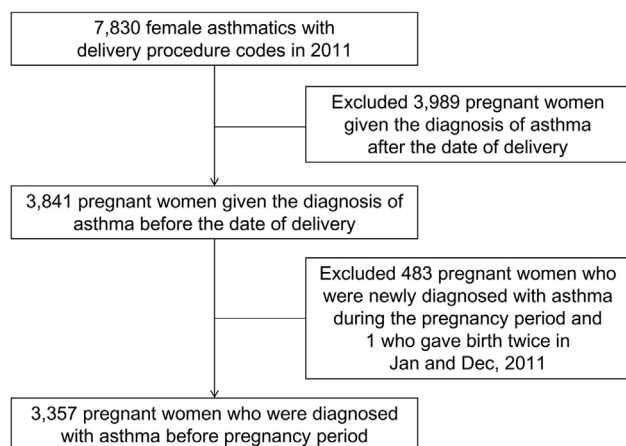


FIG 1. Flow chart of patients included in the study.

corticosteroids, were markedly lower in pregnant asthmatic patients than in nonpregnant asthmatic patients ($P < .001$), whereas ICS monotherapy was prescribed slightly more in pregnant patients. The overall proportion of pregnant patients who were prescribed at least 1 ICS-based inhaler was only around 14.6% (Table I).

We followed up the 3,357 pregnant asthmatic patients for 1 year before the pregnancy period (52 weeks), during the pregnancy period (40 weeks), and up to 2 years after delivery (104 weeks). There were no significant differences in the rate of asthma-related hospitalization (0.9% to 1.3%) and the average frequency (1.1-1.3 times) and days (per person, 8.5-10.3 days; per each admission, 7.3-7.9 days) of admission among hospitalized patients over the follow-up period. On the other hand, ED visits showed a gradual decrease from the pregnancy period through the first year after giving birth, and the rate recovered in the second year after delivery (1.0% 1 year before pregnancy, 0.4% during pregnancy, 0.2% in the first year after delivery, and 0.7% in the second year after delivery; $P < .001$). The data also indicated a noticeable decrease in outpatient visits during the pregnancy period, which increased slowly after delivery ($P < .001$). The proportion of patients prescribed asthma medication, such as ICS-based inhalers, LTRAs, SABAs, systemic LABAs, xanthine derivatives, and systemic corticosteroids, showed a drastic decrease in the pregnancy period, and most of them increased steadily over the 2 years after delivery. However, none of the prescriptions for asthma medication reverted back to prepregnancy levels until 2 years after delivery (Table II).

Next, changes in asthma-related health care use and prescriptions were assessed in the first, second, and third trimesters during pregnancy. There was a gradual increase in the proportion of patients who were ever hospitalized with the advancement of pregnancy (first trimester, 0.2%; second trimester, 0.5%; and third trimester, 0.7%; $P = .018$). The average number and days of admission per person did not differ significantly between trimesters. At the same time, ED visit rates (0.1% to 0.2%) exhibited similar patterns throughout the pregnancy period, whereas a high proportion of outpatient visits was observed in the first trimester (first trimester, 14.1%; second trimester, 10.5%; and third trimester, 10.2%; $P < .001$). The percentage of patients prescribed ICS-based inhalers, including ICS monotherapy and ICS/LABA combination inhalers, remained stable across trimesters, whereas prescriptions of other oral medications,

TABLE I. Comparison of asthma-related health care use and prescribed medications between pregnant asthmatic patients and nonpregnant asthmatic patients during pregnancy and the control period throughout 2010-2011

Characteristics	Pregnant asthmatic patients, total n = 3,357		Nonpregnant asthmatic patients,* total n = 50,355		P value
	No.	Percent	No.	Percent	
Hospitalizations					.005
Never	3,315	98.7	49,811	99.2	
Ever†	42	1.3	394	0.8	
Mean $\pm$ SD‡	1.33 $\pm$ 0.69		1.17 $\pm$ 0.53		.148
Hospitalization days§					
Per capita (mean $\pm$ SD)	10.29 $\pm$ 10.51		9.90 $\pm$ 8.79		.790
Per each admission (mean $\pm$ SD)	7.71 $\pm$ 7.16		8.44 $\pm$ 6.42		.430
ICU hospitalizations					1
Never	3,357	100	50,199	100	
Ever	0	0	6	0	
Mean $\pm$ SD			1.17 $\pm$ 0.41		
ED visits					.786
Never	3,344	99.6	49,986	99.6	
Ever	13	0.4	219	0.4	
Mean $\pm$ SD	1.08 $\pm$ 0.28		1.12 $\pm$ 0.56		.164
No. of outpatient visits					<.001
Never	2,628	78.3	32,766	65.1	
Ever	729	21.7	17,589	34.9	
1-5	640	19.1	14,342	28.5	
6-10	68	2.0	2,369	4.7	
≥ 11	21	0.6	883	1.7	
Mean $\pm$ SD	2.91 $\pm$ 3.02		3.68 $\pm$ 4.49		<.001
Prescribed medications¶					
ICS-based inhalers#	489	14.6	8,793	17.5	<.001
ICSs	236	7.0	3,001	6.0	.013
ICS/LABA combination	351	10.5	7,008	14.0	<.001
LTRAs	237	7.1	7,939	15.8	<.001
SABAs	325	9.7	6,885	13.7	<.001
Systemic LABAs	100	3.0	3,992	8.0	<.001
Xanthine derivatives	159	4.7	6,215	12.4	<.001
Systemic corticosteroids	249	7.4	8,330	16.6	<.001

*Nonpregnant asthmatic patients were matched to pregnant asthmatic patients based on 2 factors: age by decade and the presence of exacerbation history within 1 year before the period of analysis.

†Number of patients who underwent asthma-related hospitalization at least once.

‡Average number of admissions per person among patients who had asthma-related hospitalizations at least once.

§Average length of stay among patients who had asthma-related hospitalizations at least once (per person or per admission).

||Included patients who underwent asthma-related ED visits without admission.

¶Number and proportion of patients prescribed each asthma medication at least once.

#Number and proportion of patients prescribed ICSs or ICS/LABA combinations at least once.

such as LTRAs, systemic LABAs, xanthine derivatives, and systemic corticosteroids, showed a progressive decrease of around one quarter to two thirds from the first to the third trimester (Table III).

Asthma exacerbations during pregnancy and adverse perinatal outcomes

For analysis of adverse pregnancy outcomes, the population was expanded to pregnant patients who had delivered between

TABLE II. Serial observation of health care use patterns of the study population during the year before pregnancy, the pregnancy period, and 2 years after delivery

Characteristics	1 y Before pregnancy (52 wk)		Pregnancy period (40 wk)		1 y After delivery (52 wk)		2 y After delivery (52 wk)		P value
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	
Hospitalizations									.248
Never	3,316	98.8	3,315	98.7	3,327	99.1	3,328	99.1	
Ever	41	1.2	42	1.3	30	0.9	29	0.9	
Mean $\pm$ SD	1.12 $\pm$ 0.40		1.33 $\pm$ 0.69		1.17 $\pm$ 0.46		1.28 $\pm$ 0.70		.346
Hospitalization days									
Per capita (mean $\pm$ SD)	8.54 $\pm$ 6.99		10.29 $\pm$ 10.51		9.20 $\pm$ 11.41		9.31 $\pm$ 13.01		.898
Per each admission (mean $\pm$ SD)	7.61 $\pm$ 5.26		7.71 $\pm$ 7.16		7.89 $\pm$ 8.98		7.30 $\pm$ 7.41		.988
ICU hospitalizations									1
Never	3,356	100	3,357	100	3,356	100	3,356	100	
Ever	1	0	0	0	1	0	1	0	
Mean $\pm$ SD	—		—		—		—		
ED visits									<.001
Never	3,325	99.0	3,344	99.6	3,349	99.8	3,332	99.3	
Ever	32	1.0	13	0.4	8	0.2	25	0.7	
Mean $\pm$ SD	1.13 $\pm$ 0.42		1.08 $\pm$ 0.28		1.13 $\pm$ 0.35		1.44 $\pm$ 0.92		.185
No. of outpatient visits									<.001
Never	870	25.9	2,628	78.3	2,351	70.0	2,151	64.1	
Ever	2,487	74.1	729	21.7	1,006	30.0	1,206	35.9	
1-5	2,191	65.3	640	19.1	781	23.3	917	27.3	
6-10	217	6.5	68	2.0	136	4.1	176	5.2	
≥ 11	79	2.4	21	0.6	89	2.7	113	3.4	
Mean $\pm$ SD	2.83 $\pm$ 3.34		2.91 $\pm$ 3.02		4.25 $\pm$ 5.56		4.30 $\pm$ 5.03		<.001
Prescribed medications									
ICS-based inhalers	1,013	30.2	489	14.6	528	15.7	508	15.1	<.001
ICSs	447	13.3	236	7.0	221	6.6	276	8.2	<.001
ICS/LABA combination	717	21.4	351	10.5	397	11.8	420	12.5	<.001
LTRAs	939	28.0	237	7.1	488	14.5	671	20.0	<.001
SABAs	846	25.2	325	9.7	409	12.2	508	15.1	<.001
Systemic LABAs	529	15.8	100	3.0	284	8.5	314	9.4	<.001
Xanthine derivatives	808	24.1	159	4.7	324	9.7	432	12.9	<.001
Systemic corticosteroids	1,053	31.4	249	7.4	482	14.4	639	19.0	<.001

2011 and 2013 (total $n = 10,311$). A total of 546 (5.3%) patients experienced an acute asthma exacerbation at least once during the pregnancy period. We compared adverse pregnancy outcomes between the patients who experienced acute asthma exacerbations (group A, $n = 546$) and those who had no exacerbations during pregnancy (group B, $n = 9,765$) using the NHI claims database. The 2 groups did not differ significantly in the incidence of preterm labor, placenta previa, and gestational diabetes mellitus in terms of ICD-10 codes. However, preeclampsia was seen more often in patients who underwent acute asthma exacerbations during pregnancy, although this did not meet statistical significance (2.4% in group A vs 1.4% in group B, $P = .072$). The incidence of cesarean section was greater in women who had an acute asthma exacerbation than in women who had no such attack (27.1% in group A vs 18.9% in group B, $P < .001$), even after excluding cases caused by fetopelvic disproportion, failed induction, malpresentation of the fetus, known or suspected abnormality of pelvic organs, or any other direct indication for a cesarean section (7.3% vs 5.3%, $P = .049$). However, the rate of cesarean section related to fetal distress or intrauterine hypoxia was similar between the groups (1.6% vs 1.4%, $P = .727$; Table IV).

For comparison of baseline characteristics between the 2 groups before pregnancy, health care use and prescriptions in

the previous year of pregnancy were investigated. Group A had distinctly higher (statistically significant) proportions of all kinds of asthma-related health care use in terms of hospitalizations, ICU admissions, ED visits, and outpatient visits within 1 year before pregnancy compared with group B. More than half of group A asthmatic patients were prescribed at least 1 ICS-based inhaler in the previous year compared with 22.1% in group B. All other asthma medications, including systemic corticosteroids, were prescribed for more patients in group A than in group B during the year before pregnancy ($P < .001$, Table V). Prescriptions of most asthma medications, including ICS-based inhalers, in group A remained stable or higher during the pregnancy period than 1 year before pregnancy. However, prescription of asthma medications in group B significantly decreased after pregnancy from levels before (Fig 2 and see Table E3 in this article's Online Repository at www.jacionline.org).

Differences between newly diagnosed and previously diagnosed asthma during pregnancy

The 3357 enrolled patients given a previous diagnosis of asthma were compared with 483 patients with new diagnoses of asthma in pregnancy. The proportion of asthmatic patients who were hospitalized because of asthma exacerbation in the group

TABLE III. Course of asthma-related health care use and prescriptions during the 3 trimesters of the pregnancy period

Characteristics	First trimester		Second trimester		Third trimester		P value
	No.	Percent	No.	Percent	No.	Percent	
Hospitalizations							.018
Never	3,349	99.8	3,341	99.5	3,333	99.3	
Ever	8	0.2	16	0.5	24	0.7	
Mean $\pm$ SD	1.25 $\pm$ 0.71		1.13 $\pm$ 0.34		1.17 $\pm$ 0.48		.838
Hospitalization days							
Per capita (mean $\pm$ SD)	9.0 $\pm$ 7.09		8.50 $\pm$ 2.19		9.33 $\pm$ 12.93		.966
Per each admission (mean $\pm$ SD)	7.20 $\pm$ 3.05		7.56 $\pm$ 2.66		8.0 $\pm$ 9.83		.951
ICU hospitalizations							
Never	3,357	100	3,357	100	3,357	100	
Ever	0	0	0	0	0	0	
Mean $\pm$ SD	—		—		—		.842
ED visits							
Never	3,353	99.9	3,351	99.8	3,353	99.9	
Ever	4	0.1	6	0.2	4	0.1	
Mean $\pm$ SD	1 $\pm$ 0		1 $\pm$ 0		1 $\pm$ 0		<.001
No. of outpatient visits							
Never	2,882	85.9	3,004	89.5	3,013	89.8	
Ever	475	14.1	353	10.5	344	10.2	
1-5	463	13.8	344	10.2	334	9.9	
6-10	9	0.3	6	0.2	10	0.3	
≥ 11	3	0.1	3	0.1	0	0.0	
Mean $\pm$ SD	1.83 $\pm$ 1.64		1.81 $\pm$ 1.47		1.79 $\pm$ 1.18		.594
Prescribed medications							
ICS-based inhalers	265	7.9	271	8.1	273	8.1	.932
ICSs	115	3.4	118	3.5	110	3.3	.863
ICS/LABA combination	184	5.5	179	5.3	191	5.7	.812
LTRAs	156	4.6	70	2.1	79	2.4	<.001
SABAs	168	5.0	136	4.1	129	3.8	.044
Systemic LABAs	59	1.8	30	0.9	21	0.6	<.001
Xanthine derivatives	107	3.2	52	1.5	36	1.1	<.001
Systemic corticosteroids	141	4.2	79	2.4	93	2.8	<.001

TABLE IV. Adverse pregnancy outcomes in patients who experienced acute asthma exacerbations and those who had no acute asthma exacerbations during the gestational period

Adverse pregnancy outcomes	Patients who experienced acute asthma exacerbation (group A), total n = 546		Patients who had no acute asthma exacerbation (group B), total n = 9,765		P value
	No.	Percent	No.	Percent	
Preterm labor	72	13.2	1,176	12.0	.465
Preeclampsia	13	2.4	132	1.4	.072
Gestational diabetes mellitus	172	31.5	3,298	33.8	.295
Placenta previa	9	1.6	148	1.5	.947
Cesarean section, total	148	27.1	1,849	18.9	<.001
Exclude direct causes*	40	7.3	515	5.3	.049
With fetal distress or intrauterine hypoxia†	9	1.6	134	1.4	.727

*Excludes cases caused by fetopelvic disproportion, failed induction, malpresentation of the fetus, known or suspected abnormality of pelvic organs, placenta previa, or placenta abruptio.

†Includes cases that have ICD codes of fetal distress or intrauterine hypoxia only.

with newly diagnosed asthma was 2.7 times higher than in the group with previously diagnosed asthma during the pregnancy period (3.5% vs 1.3%, $P < .001$). Moreover, the incidence of outpatient visits and prescriptions for all asthma medications, including ICS-based inhalers, LTRAs, SABAs, systemic LABAs, xanthine derivatives, and systemic corticosteroids, were noticeably higher in the patients with newly diagnosed asthma ($P < .001$). About 49.5% of the patients with newly diagnosed asthma were prescribed ICSs, ICS/LABA inhalers, or both during

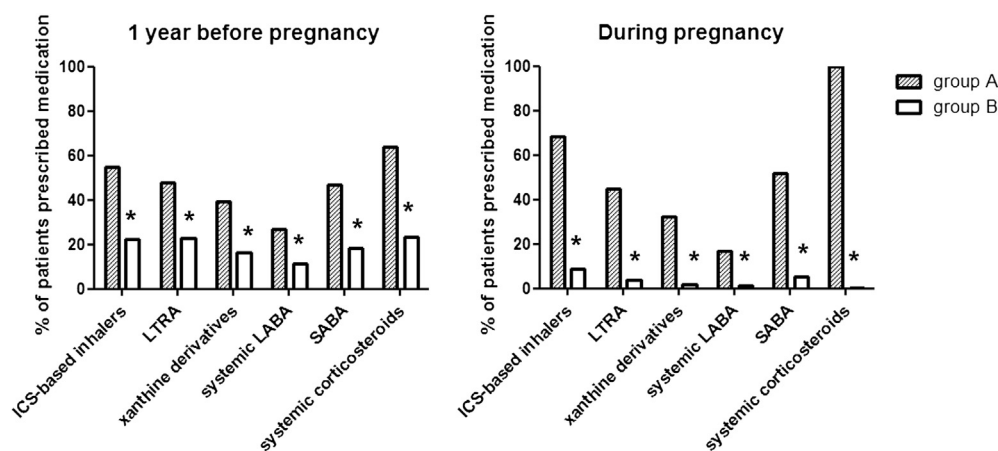
their pregnancy period compared with only about 14.6% in the patients with previously diagnosed asthma. However, ICU hospitalizations, frequencies and days of hospitalization, and ED visits did not differ between the groups (Table VI).

DISCUSSION

Using the Korean NHI claims data, we analyzed asthma-related health care use and prescription patterns in pregnant asthmatic

TABLE V. Comparison of health care use and prescriptions in the year before to the pregnancy period between patients who experienced acute attacks of asthma during pregnancy (group A) and those who had no attacks during pregnancy (group B)

Characteristics	Patients who experienced acute asthma exacerbation (group A), total n = 546		Patients who had no acute asthma exacerbation (group B), total n = 9,765		P value
	No.	Percent	No.	Percent	
Hospitalizations					<.001
Never	520	95.2	9,674	99.1	
Ever	26	4.8	91	0.9	
Mean $\pm$ SD		1.35 $\pm$ 0.63		1.09 $\pm$ 0.28	.051
Hospitalization days					
Per person (mean $\pm$ SD)		10.04 $\pm$ 9.04		7.99 $\pm$ 5.78	.282
Per each admission (mean $\pm$ SD)		7.46 $\pm$ 4.54		7.34 $\pm$ 5.06	.907
ICU hospitalizations					.016
Never	544	99.6	9,763	100	
Ever	2	0.4	2	0	
Mean $\pm$ SD		1		1	
ED visits					<.001
Never	522	95.6	9,716	99.5	
Ever	24	4.4	49	0.5	
Mean $\pm$ SD		1.63 $\pm$ 1.50		1.08 $\pm$ 0.28	.091
No. of outpatient visits					<.001
Never	77	14.1	4,133	42.3	
Ever	469	85.9	5,632	57.7	
1-5	290	53.1	5,094	52.2	
6-10	105	19.2	426	4.4	
≥ 11	74	13.6	112	1.1	
Mean $\pm$ SD		6.07 $\pm$ 6.29		2.56 $\pm$ 2.70	<.001
Prescribed medications					
ICS-based inhalers	300	54.9	2,157	22.1	<.001
ICSs	138	25.3	953	9.8	<.001
ICS/LABA combination	243	44.5	1,501	15.4	<.001
LTRAs	261	47.8	2,236	22.9	<.001
SABAs	256	46.9	1,799	18.4	<.001
Systemic LABAs	146	26.7	1,127	11.5	<.001
Xanthine derivatives	215	39.4	1,615	16.5	<.001
Systemic corticosteroids	349	63.9	2,260	23.1	<.001

**FIG 2.** Comparison of the percentage of patients prescribed asthma medications between 1 year before pregnancy and the pregnancy period. *Group A*, Patients who experienced acute asthma exacerbation during pregnancy; *group B*, patients who had no acute asthma exacerbation during pregnancy.**P* < .001. Actual data and *P* values are shown in [Table E3](#).

patients. Our study findings indicated that pregnant asthmatic patients had more asthma-related hospitalizations but significantly fewer outpatient visits and prescriptions for most asthma

medications than nonpregnant asthmatic patients. The results showed prominent decreases in outpatient visits and prescription rates in the pregnancy period compared with the year preceding

TABLE VI. Comparison of asthma-related health care use between patients with newly diagnosed asthma during pregnancy and those with previously diagnosed asthma before pregnancy

Characteristics	Newly diagnosed asthma during gestational period, total n = 483		Previously diagnosed asthma before pregnancy, total n = 3,357		P value
	No.	Percent	No.	Percent	
Hospitalizations					<.001
Never	466	96.5	3,315	98.7	
Ever	17	3.5	42	1.3	
Mean $\pm$ SD		1.18 $\pm$ 0.53		1.33 $\pm$ 0.69	.402
Hospitalization days					.095
Per person (mean $\pm$ SD)		7.41 $\pm$ 2.76		10.29 $\pm$ 10.51	.107
Per each admission (mean $\pm$ SD)		6.30 $\pm$ 2.52		7.71 $\pm$ 7.16	.207
ICU hospitalizations					.13
Never	483	100	3,357	100	
Ever	0	0	0	0.620	
ED visits					.392
Never	483	100	3,344	99.6	
Ever	0	0	13	0.4	
Mean $\pm$ SD		1.0 $\pm$ 0.0		1.08 $\pm$ 0.28	
No. of outpatient visits					<.001
Never	21	4.3	2,628	78.3	
Ever	462	95.7	729	21.7	
1-5	449	93.0	640	19.1	
6-10	10	2.1	68	2.0	
≥ 11	3	0.6	21	0.6	
Mean $\pm$ SD		1.69 $\pm$ 1.45		2.91 $\pm$ 3.02	<.001
Prescribed medications					
ICS-based inhalers	239	49.5	489	14.6	<.001
ICSs	134	27.7	236	97.0	<.001
ICS/LABA combination	135	28.0	351	10.5	<.001
LTRAs	98	20.3	237	7.1	<.001
SABAs	168	34.8	325	9.7	<.001
Systemic LABAs	40	8.3	100	3.0	<.001
Xanthine derivatives	75	15.5	159	4.7	<.001
Systemic corticosteroids	133	27.5	249	7.4	<.001

pregnancy and similar hospitalization rates throughout the pre-pregnancy until postpartum periods. Because the pregnancy period was shorter than the prepregnancy or postpregnancy periods (40 vs 52 weeks, respectively), we reanalyzed the data by applying 40 weeks equally to each period, and more patients were hospitalized during the pregnancy period than others (see [Table E4](#) in this article's Online Repository at www.jacionline.org). These results imply reduced outpatient visits and medication use of pregnant asthmatic patients during the pregnancy period might have an effect on the risk of asthma-related hospitalization during pregnancy.

Various retrospective and prospective studies have examined the course of asthma during pregnancy.²⁷⁻³⁰ Although these studies showed markedly different results depending on the method of asthma assessment and the source of study populations, the general understanding from a previous meta-analysis³¹ has been that about one third of asthmatic patients experience asthma improvement, one third experience no change, and one third experience worsening of their asthma during pregnancy. The most reliable factor to predict the course of asthma during pregnancy has been proposed as the baseline severity of asthma based on substantial evidence. Schatz et al³² found that patients with severe asthma experienced significantly more hospitalizations, unscheduled visits, and oral steroid use during pregnancy than seen in patients with mild-to-moderate asthma. A recent

study by Belanger et al³³ reported a meaningful interaction between asthma severity in the year before pregnancy and the gestational period, unlike several other factors, such as race, age, atopic status, body mass index, parity, fetal sex, and smoking, which had no effect on asthma severity during pregnancy.

Because there were not enough clinical data to assess asthma severity, which is one of the limitations of studies that use claims data, we could not evaluate the relationship between disease severity and asthma deterioration during the pregnancy period in our present study. Instead, we examined asthma-related health care use and prescriptions in the year before pregnancy and identified higher outpatient visits and prescriptions within the previous year in the asthma exacerbation group. This result indicates that patients with more severe asthma before pregnancy might experience asthma deterioration during pregnancy.

One previous study has found that the peak of all ED visits for any reason occurred during gestational weeks 6 and 7, after which the frequency of visits gradually decreased.³⁴ On the other hand, increased asthma symptoms and more frequent exacerbations seem to occur mainly in the second and third trimesters.^{23,27,35} We reaffirmed some of these findings and reported an increase in hospitalization rates in the second and third trimesters. Although the proportion of prescriptions for ICS-based inhalers showed no change throughout 3 trimesters, it is possible that an abrupt decrease in medical use and prescriptions after conception

could have had a deleterious effect on the latter part of pregnancy. In addition, we noticed a distinct reduction in prescriptions of oral controller medications over the pregnancy period, and this might reflect the fear of doctors or patients about adverse pregnancy outcomes. The decision to admit a pregnant asthmatic patient could have been precautionary in some cases and not representative of true exacerbations; however, it is important that physicians educate pregnant asthmatic patients to maintain their asthma medications for prevention of exacerbations that require hospitalization.

In the present study 5.3% of the participants experienced asthma exacerbations during pregnancy, which was similar to that reported in a meta-analysis based on 8 prospective cohort studies (5.8%; interquartile range, 2.4% to 8.2%) and a recent population-based study in the United Kingdom (approximately 5%).^{19,36} A previous large multicenter study has found that asthma exacerbation during pregnancy occurs in more than half of patients with severe asthma, whereas only 12% of patients with mild asthma have exacerbations.³² The participants of our study were enrolled from the NHI claims database, which consists of the entire Korean population, and we applied strict criteria for defining asthma-related hospitalization and ED visits by including claims that concurrently prescribed systemic corticosteroids (≥ 3 days for hospitalization and at least once for ED visits). Thus the proportion of asthmatic patients who experienced severe exacerbations requiring medical interventions, such as hospitalization, unscheduled visits, or use of emergency treatment, might have been not so high. In addition, pregnant patients' restraint concerning health care use because of concerns about the safety of asthma medications during pregnancy could be partly responsible for the relatively lower rate.

Adverse perinatal outcomes were not significantly related to exacerbations during the pregnancy period except for cesarean section in the present study. These exacerbations were all treated with systemic corticosteroids and other antiasthma medications. Furthermore, prescriptions of ICS-based inhalers and other asthma medications for patients who had acute exacerbations during pregnancy were similar or rather increased during pregnancy compared with the previous year in contrast to a significant decrease in the patient group with no asthma exacerbations. Given these results, we cautiously speculate that the risk of adverse perinatal outcomes probably will not increase in patients who experience exacerbations if appropriate care is taken.

The incidence of preeclampsia tended to increase among pregnant patients with asthma exacerbations, although it was not statistically significant. According to a meta-analysis, low birth weight was the only poor perinatal outcome associated with asthma exacerbation during pregnancy, and there were no significant associations with preterm delivery or preeclampsia.¹⁹ Interestingly, a more recent meta-analysis conducted by the same study group indicated that maternal asthma was consistently associated with an increased risk of low birth weight and preeclampsia, whereas the risks of preterm delivery and preterm labor were reduced to nonsignificant levels by active asthma management with the potential to reduce exacerbations.¹⁰ In addition, more increased risk of pregnancy-induced hypertension among uncontrolled asthma was reported by Blais et al.³⁷ The rate of cesarean section in our study subjects with asthma was 19.4% (27.1% in group A and 18.9% in group B), which was not higher than the average cesarean delivery rate of around 36% of all births

in Korea between 2011 and 2013. However, patients who had acute exacerbations during pregnancy were more likely to undergo cesarean section than those who had not, and the significance was maintained, even after excluding certain indications for elective cesarean section or failed induction. However, the rate of cesarean section combined with fetal stress or intrauterine hypoxia was shown to be unrelated to asthma exacerbations. Therefore large-scale research is needed to clarify the effect of asthma control on the delivery method because cesarean section could have been preferred for patients who experienced exacerbation in apprehension for complications. Unfortunately, data on birth weights of newborns of asthmatic women were not obtained in this study.

One of the noteworthy findings from this study was that patients with newly diagnosed asthma during the gestational period had more hospitalizations and outpatient visits, as well as a higher percentage of drug prescriptions in their pregnancy period, compared with patients with pre-existing asthma. This contrasted with our previous findings from another study that was conducted in the entire group of asthmatic patients using the same NHI claims data, which identified lower asthma-related hospitalizations in the patients with newly diagnosed asthma.²⁶ One possible explanation for these results is that a portion of the patients with newly diagnosed asthma might have received their diagnoses some time before the study period and not have made regular follow-up visits, supporting the idea that nonadherence is the culprit for asthma exacerbations during pregnancy.^{23,24} Another possible assumption might be that the concerns for adverse pregnancy outcome associated with asthma could be higher in patients with newly diagnosed asthma.

Some limitations of our study resulted from the use of administrative claims data. First, the data used for the study had no clinical information to assess asthma severity and potential confounders, such as maternal lifestyle risk factors or comorbid conditions. Second, it is possible that some asthmatic patients with less severe symptoms or limited access to a medical center did not seek medical advice, leading to an underestimation of the proportion of asthmatic patients. Third, we lack information on actual drug use apart from prescriptions and could not evaluate adherence to medications.

Despite these limitations, asthma-related health care patterns reflecting real-world practice for pregnant asthmatic patients were evaluated in our current analyses. We confirmed that pregnant asthmatic patients had more asthma-related hospitalizations than nonpregnant asthmatic patients, which could result from prominent reduction of outpatient visits or prescribed medications after pregnancy. Patients with more severe asthma have asthma deterioration, even when prescriptions remain stable during pregnancy, whereas patients with mild asthma do not experience severe exacerbations despite the reduction in prescriptions. However, asthma exacerbation during pregnancy did not seem to be related to the increased risk of poor perinatal outcomes, except for cesarean section, when it was managed appropriately. To reach a more robust conclusion, further clinical investigations, including exacerbation severity and other management, such as oxygen during exacerbation, are required. Also, a new approach to study the effect of different behaviors on adverse pregnancy outcomes according to their asthma severity is needed to present more advanced practice guidelines for both pregnant asthmatic patients and physicians.

Key messages

- Pregnant asthmatic patients had more asthma-related hospitalizations but fewer outpatient visits and prescriptions for asthma medications than nonpregnant asthmatic patients.
- Asthma exacerbation during pregnancy was not related to poor perinatal outcomes, except for cesarean delivery, when it was managed appropriately with systemic corticosteroids.

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METHODS

Outcome measures

We compared asthma-related health care use and prescribed asthma medication between pregnant asthmatic patients and nonpregnant female asthmatic control subjects. The analysis period was applied individually for pregnant asthmatic patients as the pregnancy period over 2010 to 2011 on the basis of their date of delivery, whereas the period of 40 weeks before a fixed date (June 30, 2011) was applied as the control period of nonpregnant control subjects. The presence of acute exacerbation of asthma was evaluated during 1 year before the analysis period to match the baseline disease severity of the 2 patient groups (Fig E1). To investigate patterns of asthma-related health care use, we counted the number of asthma-related claims that contained prescriptions of asthma-related medications or laboratory tests at outpatient visits, hospitalizations, ICU hospitalizations, and ED visits. For hospitalizations, ICU hospitalizations, and ED visits, only the claims that prescribed systemic corticosteroids (oral or intravenous) were defined as asthma-related claims to exclude any visits that were not specifically caused by asthma; a prescription of systemic corticosteroids of at least 3 days was required for hospitalizations and ICU hospitalizations, and 1 or more prescription of systemic corticosteroids was required for ED visits to be qualified as asthma-related claims.

We investigated the claims data of pregnant asthmatic patients throughout a total of almost 4 years: 1 year before pregnancy, during the pregnancy period, and 2 years after delivery. The pregnancy period was further sectioned into 3 trimesters as the first (0-13 weeks), second (14-26 weeks), and third (27-40 weeks) trimesters to investigate trends in asthma-related health care use and prescription of asthma medication.

Adverse pregnancy outcomes of patients who experienced acute asthma exacerbation during the pregnancy period were compared with those of patients who had no acute asthma exacerbations. ICD-10 codes of preterm labor, placenta previa, preeclampsia, gestational diabetes mellitus, and cesarean section were evaluated. The incidence of cesarean section was analyzed after excluding cases caused by fetopelvic disproportion, failed induction, malpresentation of fetus, or any other direct indication for a cesarean section from the total number of cases. Also, the cases with ICD-10 codes of fetal distress or intrauterine hypoxia were evaluated.

In addition, we compared the differences in asthma-related health care use and prescription patterns between patients who were given a diagnosis of asthma before their pregnancy period ($n = 3,357$) and patients with newly diagnosed asthma during their pregnancy period ($n = 483$, Fig 1).

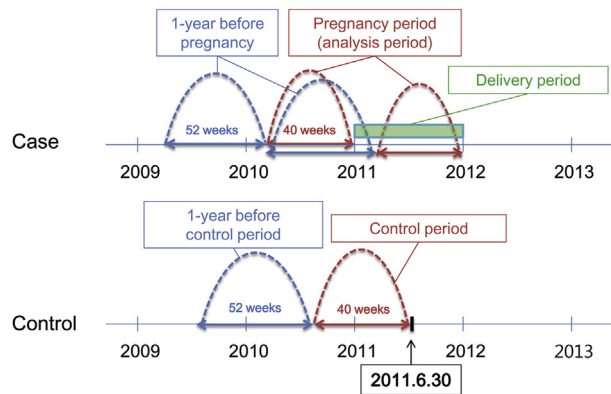


FIG E1. Schematic diagram of observation periods of pregnant asthmatic patients and nonpregnant asthmatic control subjects.

TABLE E1. Procedure codes related to delivery for the Korean health insurance system

Categorization		Procedure codes
Spontaneous delivery	Delivery	R3131, R3133, R3136, R3138, R3141, R3143, R3146, R3148, R4351, R4353, R4356, R4358, RA311-318, RA431-434
	Breech delivery	R4361-4362, RA361-362
	Vaginal birth after cesarean section	R4380, RA380
Delivery by cesarean section	Midwifery fee	V0111-0112, V0121-0122, V0131-0132
	Cesarean section delivery	R4514-4520
	Cesarean hysterectomy	R4507-4510, R5001-5002

TABLE E2. Matching table of cases and control subjects in [Table I](#)

Patient classification		Pregnant asthmatic patients (case [no.])	Nonpregnant asthmatic patients (control subjects [no.])	Control/case ratio	Matched nonpregnant asthmatic control subjects (1:15)
Age by decade	Asthma exacerbation				
20-29 y	A	1,116	18,666	16.7	16,740
	P	493	7,633	15.5*	7,395
30-39	A	1,183	32,202	27.2	17,745
	P	533	14,445	27.1	7,995
40-49	A	17	41,948	2467.5	255
	P	15	18,295	1219.7	225
Total no.		3,357			50,355

A, Absence of acute asthma exacerbation for 1 year before the period of analysis; P, presence of acute asthma exacerbation for 1 year before the period of analysis.

*Lowest control/case ratio.

TABLE E3. Comparison of the percentage of patients who were prescribed asthma medications between 1 year before pregnancy and the pregnancy period

Prescribed medications	1 y Before pregnancy		During pregnancy		P value
	No.	Percent	No.	Percent	
Group A (total n = 546)					
ICS-based inhalers	300	54.9	373	68.3	<.001
ICSs	138	25.3	210	38.5	<.001
ICS/LABA combination	243	44.5	278	50.9	.039
LTRAs	261	47.8	244	44.7	.331
Xanthine derivatives	215	39.4	175	32.1	.014
Systemic LABAs	146	26.7	93	17.0	<.001
SABAs	256	46.9	282	51.6	.130
Systemic corticosteroids	349	63.9	546	100	<.001
Group B (total n = 9,765)					
ICS-based inhalers	2,157	22.1	855	8.8	<.001
ICSs	953	9.8	404	4.1	<.001
ICS/LABA combination	1,501	15.4	577	5.9	<.001
LTRAs	2,236	22.9	383	3.9	<.001
Xanthine derivatives	1,615	16.5	190	1.9	<.001
Systemic LABAs	1,127	11.5	132	1.4	<.001
SABAs	1,799	18.4	517	5.3	<.001
Systemic corticosteroids	2,157	22.1	855	8.8	<.001

Group A, Patients who experienced acute asthma exacerbation during pregnancy;

group B, patients who had no acute asthma exacerbation during pregnancy.

TABLE E4. Serial observation of health care use patterns of the study population during the 40 weeks before pregnancy, the pregnancy period, and 80 weeks after delivery (adjusted from [Table II](#))

Characteristics	40 wk Before pregnancy		Pregnancy period (40 wk)		40 wk After delivery		40-80 wk After delivery		P value
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	
Hospitalizations									.013
Never	3,321	98.9	3,315	98.7	3,332	99.3	3,338	99.4	
Ever	36	1.1	42	1.3	25	0.7	19	0.6	
Mean $\pm$ SD	1.06 $\pm$ 0.23		1.33 $\pm$ 0.69		1.16 $\pm$ 0.47		1.21 $\pm$ 0.63		.152
Hospitalization days									
Per capita (mean $\pm$ SD)	7.94 $\pm$ 6.32		10.29 $\pm$ 10.51		9.76 $\pm$ 12.33		8.47 $\pm$ 9.45		.727
Per each admission (mean $\pm$ SD)	7.53 $\pm$ 5.56		7.71 $\pm$ 7.16		8.41 $\pm$ 9.68		7.00 $\pm$ 9.01		.927
ICU hospitalizations									1
Never	3,356	100	3,357	100	3,356	100	3,357	100	
Ever	1	0	0	0	1	0	0	0	
Mean $\pm$ SD	—		—		—		—		
ED visits									.017
Never	3,333	99.3	3,344	99.6	3,350	99.8	3,342	99.6	
Ever	24	0.7	13	0.4	7	0.2	15	0.4	
Mean $\pm$ SD	1.13 $\pm$ 0.34		1.08 $\pm$ 0.28		1.14 $\pm$ 0.38		1.27 $\pm$ 0.59		.639
No. of outpatient visits									<.001
Never	1,220	36.3	2,628	78.3	2,512	74.8	2,346	69.9	
Ever	2,137	63.7	729	21.7	845	25.2	1,011	30.1	
1-5	1,926	57.4	640	19.1	694	20.7	823	24.5	
6-10	163	4.9	68	2.0	105	3.1	117	3.5	
≥ 11	48	1.4	21	0.6	46	1.4	71	2.1	
Mean $\pm$ SD	2.62 $\pm$ 2.86		2.91 $\pm$ 3.02		3.76 $\pm$ 4.57		3.73 $\pm$ 4.43		<.001
Prescribed medications									
ICS-based inhalers	888	26.5	489	14.6	460	13.7	470	14.0	<.001
ICSs	382	11.4	236	7.0	180	5.4	195	5.8	<.001
ICS/LABA combination	628	18.7	351	10.5	355	10.6	356	10.6	<.001
LTRAs	797	23.7	237	7.1	393	11.7	517	15.4	<.001
SABAs	719	21.4	325	9.7	330	9.8	379	11.3	<.001
Systemic LABAs	439	13.1	100	3.0	222	6.6	252	7.5	<.001
Xanthine derivatives	686	20.4	159	4.7	251	7.5	335	10.0	<.001
Systemic corticosteroids	883	26.3	249	7.4	386	11.5	495	14.7	<.001