Ophthalmic Corticosteroids in Pregnant Women with Allergic Conjunctivitis and Adverse Neonatal Outcomes: Propensity Score Analyses

YOHEI HASHIMOTO, NOBUAKI MICHIHATA, HAYATO YAMANA, DAISUKE SHIGEMI, KOJIRO MORITA, HIROKI MATSUI, HIDEO YASUNAGA, AND MAKOTO AIHARA

• PURPOSE: The risks of topical ophthalmic corticosteroids during pregnancy remain unclear. This study investigated the association between exposure to topical ophthalmic corticosteroids during pregnancy and adverse neonatal outcomes.

• DESIGN: Retrospective, cohort, database study.

• METHODS: Pregnant women with allergic conjunctivitis in the JMDC claims database (JMDC, Tokyo, Japan) between 2005 and 2018 were included. Adverse neonatal outcomes (congenital anomalies [CA], preterm birth [PB], low birthweight [LB], and the composite of these 3 outcomes) were compared between mothers who did and did not receive topical ophthalmic corticosteroids during the first trimester. Controls were women who were not prescribed topical ophthalmic corticosteroids during the first trimester. First, propensity scores were calculated with known confounders, including disorders during pregnancy, other chronic comorbidities, and use of antihistamines. Logistic regression was then conducted with propensity score adjustment.

• RESULTS: A total of 6,847 eligible women were identified of whom 898 (13%) had received topical ophthalmic corticosteroids. CA occurred in 5.5% and 4.9%, respectively; PB in 3.4% and 3.9%, respectively; LB in 5.9% and 7.0%, respectively; and the composite outcome in 11.7% and 11.7% of unexposed and exposed mothers, respectively. Corticosteroid eye drops were not significantly associated with an increase in CA (adjusted odds ratio [aOR], 0.78; 95% confidence interval [CI], 0.54-1.14; $P = .20$); PB (aOR, 1.23; 95% CI, 0.80-1.88; $P = .35$); LB (aOR, 1.17; 95% CI, 0.84-1.61; $P = .35$), or composite outcome (aOR, 0.95; 95% CI, 0.73-1.22; $P = .68$).

• CONCLUSIONS: The use of topical ophthalmic corticosteroids in pregnant women with allergic conjunctivitis was not associated with any increase in CA, PB, or LB. (Am J Ophthalmol 2020;220:91–101. © 2020 Elsevier Inc. All rights reserved.)

ALLERGIC CONJUNCTIVITIS (AC) IS COMMONLY SEEN in clinical practice, with an estimated prevalence ranging from 6% to 30%,[1,2] and up to 40% in some studies in the United States[3] and up to 35% in Eastern Europe and the Middle East.[4] AC induces itching, tearing, and redness, significantly reducing both ocular and general quality of life.[5,6] Patients with AC thus seek medications such as antihistamines and corticosteroids to control these symptoms.

Although women of child-bearing age can experience AC, suppressing the symptoms in pregnant women presents a challenge because ophthalmologists need to consider the possible adverse effects of ophthalmic medications on the mother and fetus. When such medications are absorbed through the ocular mucous membranes, they do not undergo first-pass metabolism in the liver,[7] and even locally administered medications might thus induce side effects in the fetus. The U.S. Food and Drug Administration divided drugs into 5 risk categories during pregnancy: A, B, C, D, and X.[7] Corticosteroids are categorized as group C,[7] indicating that they have demonstrated adverse effects on the fetus in animal studies, but no adequate human studies have been reported. Although some studies found that oral and systemic corticosteroids may be associated with adverse neonatal outcomes such as low birthweight,[8] preterm birth,[9,10] and anomalies,[11] other studies reported conflicting results,[12–14] with no current consensus.[15] Furthermore, no studies have yet investigated the association between ophthalmic corticosteroids and adverse neonatal outcomes. However, information for the safety of ophthalmic corticosteroids (eye drops and ointment) in pregnant women may help to reduce anxiety regarding their use in those with AC.

This study aimed to investigate the association between exposure to ophthalmic corticosteroids during pregnancy and adverse neonatal outcomes, including congenital

Accepted for publication Jul 8, 2020.

From the Department of Ophthalmology (Y.H., M.A.), Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; Department of Clinical Epidemiology and Health Economics (Y.H., D.S., K.M., H.M., H.Y.), School of Public Health, The University of Tokyo, Tokyo, Japan; and the Department of Health Services Research (N.M., H.Y.), Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

*Kojiro Morita current affiliation: Department of Health Services Research, Faculty of Medicine, University of Tsukuba and Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan.

Inquiries to: Yohei Hashimoto, Department of Ophthalmology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; e-mail: youhashimoto-tky@umin.ac.jp

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.07.011

TABLE 1. ICD-10 Codes for Neonatal Outcomes

Outcome	ICD-10 codes
Congenital anomaly	Q00-Q99 excluding codes of minor congenital anomaly: Q08-Q10, Q162, Q17-Q19, Q250, Q270, Q381, Q515, Q516, Q52-Q53, Q664-Q666, Q689, Q70, Q81-Q84, Q94-Q95.
Preterm birth	
Gestational age (22-27 wk)	P07.2
Gestational age (28-36 wk)	O60.1, O60.3, P07.3
Low birthweight	P07.0, P07.1

ICD-10 = 10th revision of the International Statistical Classification of Diseases. World Health Organization, Basel, Switzerland.

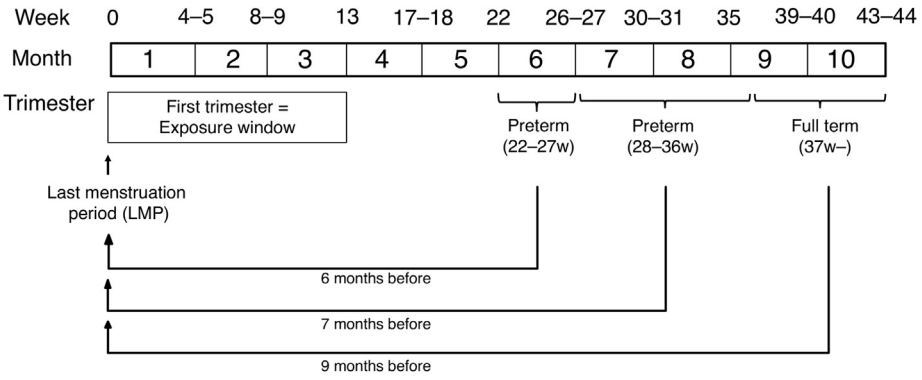

FIGURE 1. Identification of the first trimester.

anomalies, preterm birth, and low birthweight, by using a large claims database.

METHODS

• **DATA SOURCE:** A retrospective cohort study was conducted using the JMDC claims database (JMDC Inc., Tokyo, Japan) from 2005 to 2018.[16] This database stores de-identified and individual-level data for both outpatients and inpatients. In 2018, the JMDC collected health insurance claims data for >5 million people from more than 200 relatively large Japanese companies. The JMDC database included the following information for each individual: 1) unique identifier; 2) family identifiers; 3) patient characteristics (age and sex); 4) codes and dates of diagnoses (codes are based on International Classification of Diseases, 10th revision [ICD-10]); 5) codes and dates of procedures performed; 6) codes and dates of drug prescribed (codes based on the Anatomical Therapeutic Chemical Classification System [ATC]); 7) the period from the start to end of the insurance; and 8) the relationship to the insured individual (main insured, spouse, or child). This study was in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Tokyo. The need for informed consent was waived because of the anonymous nature of the database.

• **PATIENT SELECTION:** Family identifiers were used to link newborns to their mothers. Newborn babies were divided into 3 categories according to gestational age (preterm birth: 22-27 weeks; preterm birth: 28-36 weeks; and full-term birth: ≥37 weeks) by using ICD-10 codes (Table 1). The month of the last menstrual period was defined for these 3 categories as 6, 7, and 9 months before the month of delivery, respectively.[17] The first 3 months from the last menstrual period were also defined as the first trimester (gestational weeks: 0-13) (Figure 1).

Women were excluded who had enrolled for insurance <6 months before the last menstrual period to investigate potential confounders during that period. Newborn babies were also excluded who had been followed for <6 months to investigate neonatal adverse outcomes during that period.[18] Additionally, working women were excluded with an insurance status of "main insured," because they often quit their jobs and thus lost their insurance when they became pregnant, thus preventing us from obtaining follow-up data. Therefore

TABLE 2. ATC Codes For Known Fetotoxic Medications

Teratogen	ICD-10 codes
Systemic retinoids	D10BA01, D05BB02, D05BB01, A11CA01, L01XX25
Antiepileptics	S01EC01, N03AF01, N03AF04, N03AD01, N03AD51, N03AX12, N03AX18, N03AX09, N03AX14, N03AF02, N03AX22, N03AA01, N03AA02, N03AB04, N03AB05, N03AB54, N03AB02, N03AB52, N03AX16, N03AA03, N03AG01, N03AF03, N03AX11, N03AX17, N03AG06, N03AX11, N03AG04, N03AX15
Antithyroid drugs	H03BB02, H03BB52, H03BA02
Anticoagulants	B01AA03
Tetracycline derivative	B01AA07, J01AA02, J01AA08, J01GA, J01GA01, A07AA04, J04AM01, A07AA54, J01A, J01AA, A02BD08, J01AA03, J01AA20, A02BD02, G01AA07, J01AA06, J01AA56, J01AA09, A01AB13, J01AA07, nJ01RA08
Angiotensin-converting enzyme inhibitors	C09AA07, C09AA01, C09BA01, C09AA09, C09BA09, C10BX15, C10BX12, C10BX11, C09AA04, C09BB04, C09BX02, C09BA04, C09BX01, C10BX14, C10BX13, C09AA06, C09BA06, C10BX06, C09AA05, C09BB07, C09BA05, C09BB05, C09BX03, C10BX04, C09AA10, C09BB10, C09BB10, C08DA01, C08DA51
Angiotensin-receptor blocker	C09CA06, C09DB07, C09DA06, C09DX06, C09CA02, C09DA02, C09CA04, C09DB05, C09DA04, C09CA04, C09DB05, C09DA04, C09CA01, C09DB06, C09DA01, C09CA08, C09DB02, C09DA08, C09DX03, C09CA07, C09DB04, C09DA07, C09CA03, C10BX10, C09DX02, C09DB01, C09DA03, C09DB08, C09DX05
Androgens	G03XA01, G04CB, G03FA05, G03BA02, G03EK01, G03EA01, G03BA03, G03EA02, G03BA02, G03EK01, G03EA01
Antineoplastic agents	L02BG03, L02BB03, L02AE51, L02AE01, L01AB01, L01AA02, L01AA01, L01XX11, L01CB01, L02BG06, L01BC02, L01BC52, L02BB01, L02AE03, L01XX05, L01AA06, L03AB12, L03AB14, L03AB05, L03AB10, L03AB60, L03AB15, L02BG04, L02AE02, L02AE51, L01AA03, L01BB02, L01BA01, L04AX03, L02BB02, L01XB01, L02BA01, L01BB03, L01XX22, L01XX14, L02AE04
Statins	C10AA05, C10BX08, C10BX03, C10BA05, C10BX15, C10BX12, C10BX06, C10BX11, C10AA06, C10AA04, C10AA02, C10BA01, C10AA03, C10BX02, C10BA03, C10AA07, A10BH52, C10BX05, C10BX09, C10BA06, C10BX10, C10BX07, C10BX14, C10BX13, C10AA01, C10BX01, C10BA02, C10BA04, C10BX04, A10BH51
Benzodiazepines	N05BA12, N05BA08, N05BA02, N05BA09, N05BA01, N05BA17, N05CD01, N05BA06, N05BA56, N05CD03, N05CD02, N05BA04, N05CD07, N05CD05
Others	C01BD01, G03CB02, G03CC05, L02AA01, J01RA07, D01AC15, J02AC01, L04AA13, N05AN, N05AN01, D11AX04, L01BA01, L04AX03, M01CC, M01CC01, L01AA01, A02BB01, G02AD06, M01AE56, M09AA, M09AA01, P01BC01, M09AA72

ICD-10 = 10th revision of the International Statistical Classification of Diseases. World Health Organization, Basel, Switzerland.

only women with an insurance status of "spouse" (dependent family member) before pregnancy were included because they were unlikely to change their insurance status, and therefore their follow-up data. Women were then identified whose diagnosis was AC, including seasonal AC, perennial AC, vernal atopic conjunctivitis, and giant papillary conjunctivitis (corresponding to ICD-10 codes H101 and H104) during the period between 6 months before pregnancy and the end of the first trimester. Those who had been exposed to known teratogenic drugs during the first trimester were excluded from among this group (Table 2).[19] This period was considered vital for normal fetal development because most birth anomalies occur during this period.[18,20] Furthermore, women were excluded who received systemic, inhaled, intranasal, or periocular (sub-Tenon) corticosteroids by using ATC codes to allow focus on the effects of ophthalmic corticosteroids (Table 3). Finally, women with uveitis, scleritis, rheumatoid arthritis, or systemic lupus erythematosus were excluded because these autoimmune diseases themselves could have adverse neonatal outcomes[21,22] and because the steroids might have been used to the treat these diseases rather than AC.

• OUTCOMES: We defined the outcomes as congenital anomaly, preterm birth, low birthweight, and the composite of these 3 outcomes during the 6 months after delivery, based on relevant ICD-10 codes (Table 1).[11] Pregnancies were excluded that resulted in neonates with minor anomalies alone because such anomalies might not have been associated with medication use during pregnancy, as reported in a previous study.[20]

TABLE 3. ATC Codes for Corticosteroids

Generic Name	ATC Codes
Corticosteroid eye drops	
Dexamethasone	S01BA01, S03BA01
Hydrocortisone	S01BA02
Fluorometholone	S01BA07
Prednisolone	S01BA04
Betamethasone	S01BA06, S03BA03
Hydrocortisone and antibiotics, combinations	S01CA03
Betamethasone and antibiotics, combinations	S03CA06
Corticosteroid ointment	
Dexamethasone	S01BA01
Prednisolone	S01BA04
Betamethasone and antibiotics, combinations	S03CA06
Methylprednisolone and antibiotics, combinations	S01CA08
Intranasal corticosteroid	R01AD
Inhaled corticosteroid	R03BA, R03AK, R03AC12, R03AC13
Systemic corticosteroid	H02

ATC = Anatomical Therapeutic Chemical Classification System.

TABLE 4. ICD-10 and ATC Codes for Potential Confounders

Disease name	ICD-10 codes	ATC codes
Disorders during pregnancy		
Hypertensive disorders of pregnancy	O10-O16	NA
Gestational diabetes	O24	NA
Multiple pregnancy	O30, O84	NA
Chronic comorbidities		
Anemia	D50-D53	B03
Asthma	J45	R03
Hypertension	I10-I15	C02, C03, C04, C07, C08, C09, C10BX03-C10BX15
Diabetes mellitus	E10-14	A10A, A10B, A10X
Dyslipidemia	E78	C10A, C10B
Gastroduodenal ulcer	K25-K26	A02B
Thyroid disorders	E00-E07	H03
Epilepsy	G40	N03
Depression and anxiety	F30-F34, F38-F41, F43	N05B, N06
Alcohol dependence	F10	NA
Tobacco dependence	F17	NA
Other drugs dependence	F11-F12, F14-F16, F18-F19	NA
Antihistamines (eye drops)	NA	S01GX02, S01GX08, S01GX09, S01GX10
Antihistamines (oral)	NA	R06AA, R06AB, R06AC, R06AD, R06AE, R06AK, R06AX, R01AC, R01AC08, R06AD07, R06AE06, R06AE07, R06AE09, R06AX, R06AX13, R06AX17, R06AX19, R06AX22, R06AX24, R06AX26, R06AX27, R06AX28, R06AX29

ATC = Anatomical Therapeutic Chemical Classification System; ICD-10 = 10th revision of the International Statistical Classification of Diseases. World Health Organization, Basel, Switzerland; NA = not available.

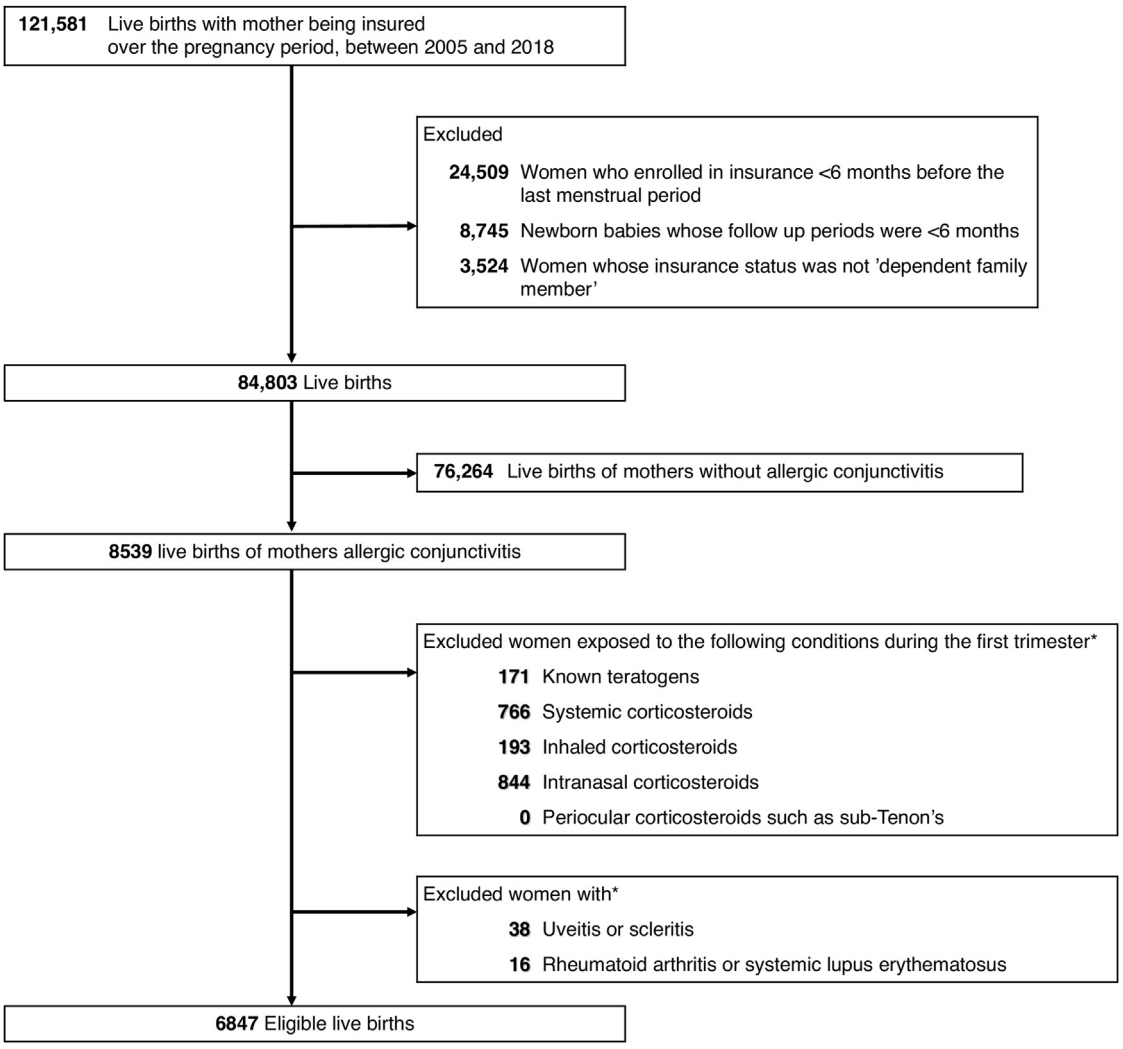

FIGURE 2. Patient selection. * Some women had multiple conditions.

• **EXPOSURE:** We defined the following levels of exposure: at least 1 prescription of 1) any corticosteroid eye drops (fluorometholone, betamethasone, dexamethasone, or hydrocortisone); 2) fluorometholone 0.1% eye drops; 3) betamethasone 0.1% eye drops; 4) dexamethasone 0.1% eye drops; 5) any corticosteroid ointment (prednisolone or dexamethasone); and 6) prednisolone ointment, with no other ophthalmic corticosteroids during the first trimester. Eye drops and ointments were excluded that were mixtures of corticosteroids and antibiotics because the aim of the study was to clarify the effect of corticosteroids. ATC codes were used to identify each ophthalmic corticosteroid (Table 3).

Notably, it was difficult to count the exact number of antihistamine prescriptions because oral and topical antihistamines can be obtained over the counter in Japan and other countries.[6,23] Therefore only the use of antihistamines was considered as one potential confounder rather than exposures.

• **POTENTIAL CONFOUNDERS:** The following variables were used as potential confounders[19,24,25]: 1) mother's age; 2) diseases during pregnancy (hypertensive disorders of pregnancy, gestational diabetes, and multiple pregnancy); 3) other chronic comorbidities (hypertension, diabetes mellitus, thyroid disorders, dyslipidemia, asthma, anemia, dyslipidemia, and gastroduodenal ulcer, epilepsy, depression, and dependence on alcohol, tobacco, or drugs); and 4) antihistamines (eye drops and oral), using ICD-10 and ATC codes (Table 4). Any woman with both the relevant ICD-10 and ATC codes during the period between 6 months before the last menstrual period and the month of delivery were considered to have these chronic comorbidities, as described previously.[18]

• **STATISTICAL ANALYSIS:** Baseline characteristics were compared between women with and without exposure to ophthalmic corticosteroids using *t*-tests for continuous

TABLE 5. Ophthalmic Corticosteroids Prescribed During the First Trimester

	n_1 (%)[a]	n_2 (%)[b]
Women with allergic conjunctivitis	6,847 (100)	-
Corticosteroid eye drops or ointment	898 (13.0)	-
Corticosteroid eye drops		
Any of the below	803 (11.7)	700 (10.2)
Betamethasone 0.1%	240 (3.5)	198 (2.9)
Betamethasone 0.01%	4 (0.1)	3 (0.0)
Dexamethasone 0.1%	80 (1.2)	64 (0.9)
Dexamethasone 0.02%	10 (0.1)	8 (0.1)
Fluorometholone 0.1%	402 (5.9)	335 (4.9)
Fluorometholone 0.05%	26 (0.4)	19 (0.3)
Fluorometholone 0.02%	91 (1.3)	73 (1.1)
Hydrocortisone 0.5%	2 (0.0)	0 (0.0)
Corticosteroid ointment		
Any of the below	65 (0.9)	35 (0.5)
Prednisolone	55 (0.8)	31 (0.5)
Dexamethasone	11 (0.2)	4 (0.1)
Corticosteroids combined with antibiotics		
Betamethasone eye drops	34 (0.5)	25 (0.4)
Betamethasone ointment	15 (0.2)	8 (0.1)
Methylprednisolone ointment	45 (0.7)	25 (0.4)
No ophthalmic corticosteroids	5949 (87)	-

[a]Women who received the medication at least once (use of other ophthalmic corticosteroids permitted).
[b]Women who received the medication at least once (use of other ophthalmic corticosteroids not permitted).

variables such as age and chi-squared tests for categorical variables such as presence or absence of anemia. Adverse neonatal outcomes (congenital anomaly, preterm birth [<37 weeks], low birthweight, and composite outcome) were compared between babies born to women with and those born to women without exposure to ophthalmic corticosteroids by using propensity score (PS) adjustment analysis. First, logistic regression analysis was conducted with the use of corticosteroid eye drops regressed against the potential confounders. Second, the impact of corticosteroid eye drop use was estimated on neonatal adverse outcomes by constructing a logistic regression model with PS adjustment, with adverse neonatal outcomes regressed against use of corticosteroid eye drops and PS. We used PS adjustment analysis rather than conventional logistic regression because PS analysis is less biased and more robust than conventional logistic regression when the number of events per confounder is small, as in the current study.[26]

Similarly, adverse neonatal outcomes were compared between babies born to women without exposure to ophthalmic corticosteroids and those exposed to fluorometholone 0.1% eye drops, betamethasone 0.1% eye drops, or dexamethasone 0.1% eye drops alone, any corticosteroid ointment (prednisolone or dexamethasone), and prednisolone ointment alone.

RESULTS

A PATIENT SELECTION FLOWCHART IS SHOWN IN FIGURE 2. After exclusion of patients according to observation period and insurance status, 84,803 live births were identified, including 8,539 women (10%) with AC. Finally, 6,847 eligible women were identified after applying the exclusion criteria.

The numbers of women who received each ophthalmic corticosteroid are shown in Table 5. Of the 6,847 eligible women, 898 (13%) received an ophthalmic corticosteroid. The most frequently prescribed corticosteroid eye drops were fluorometholone 0.1% (n = 402 [5.9%]), followed by betamethasone 0.1% (n = 240 [3.5%]). The most frequently prescribed corticosteroid ointment was prednisolone (n = 55 [0.8%]). In contrast, 5,949 women (87%) were not exposed to any ophthalmic corticosteroids during the first trimester. The numbers of women who received each medication alone are also shown in Table 5.

The baseline characteristics of the women with and without exposure to ophthalmic corticosteroids are shown in Table 6. Women in the exposed group were more likely to receive antihistamines and to have asthma than women not exposed to any corticosteroid eye drops. There were no significant differences in the other confounders between the 2 groups. The comparison between women with and

TABLE 6. Baseline Characteristics of Women with and without Exposure to Corticosteroid Eye Drops

		Exposed to corticosteroid eye drops					Exposed to corticosteroid ointment		
	Unexposed	Any[a]	*P* (Unexposed vs. Any)	Fluorometholone 0.1% alone	Betamethasone 0.1% alone	Dexamethasone 0.1% alone	Any[b]	*P* (Unexposed vs. Any)	Prednisolone alone
	n = 5,949	n = 700		n = 335	n = 198	n = 64	n = 35		n = 31
Age, y	33.1 ± 4.2	33.2 ± 4.5	.45	33.0 ± 4.6	33.4 ± 4.5	33.7 ± 4.5	33.4 ± 3.6	.61	33.5 ± 3.1
Disorders during pregnancy									
Multiple pregnancy	115 (1.9)	16 (2.3)	.62	12 (3.6)	4 (2.0)	0 (0.0)	0 (0.0)	.83	0 (0.0)
Hypertensive disorders of pregnancy	419 (7.0)	54 (7.7)	.57	22 (6.6)	20 (10.1)	4 (6.2)	2 (5.7)	1.00	2 (6.5)
Gestational diabetes	325 (5.5)	37 (5.3)	.91	16 (4.8)	11 (5.6)	6 (9.4)	1 (2.9)	.76	1 (3.2)
Chronic comorbidities									
Anemia	3038 (51.1)	356 (50.9)	.95	177 (52.8)	89 (44.9)	25 (39.1)	20 (57.1)	.58	17 (54.8)
Asthma	657 (11.0)	102 (14.6)	.007	41 (12.2)	39 (19.7)	9 (14.1)	2 (5.7)	.46	2 (6.5)
Hypertension	91 (1.5)	11 (1.6)	1.00	5 (1.5)	3 (1.5)	1 (1.6)	0 (0.0)	.96	0 (0.0)
Diabetes mellitus	35 (0.6)	6 (0.9)	.55	2 (0.6)	1 (0.5)	2 (3.1)	0 (0.0)	1.00	0 (0.0)
Dyslipidemia	11 (0.2)	1 (0.1)	1.00	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1.00	0 (0.0)
Gastroduodenal ulcer	276 (4.6)	39 (5.6)	.32	20 (6.0)	9 (4.5)	3 (4.7)	1 (2.9)	.92	1 (3.2)
Thyroid diseases	133 (2.2)	13 (1.9)	.61	6 (1.8)	5 (2.5)	2 (3.1)	1 (2.9)	1.00	1 (3.2)
Epilepsy	18 (0.3)	1 (0.1)	.71	10 (3.0)	8 (4.0)	3 (4.7)	0 (0.0)	.69	0 (0.0)
Depression and anxiety	148 (2.5)	24 (3.4)	.18	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00	0 (0.0)
Dependence (tobacco, alcohol, or drugs)	5 (0.1)	0 (0.0)	.97	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1.00	0 (0.0)
Antihistamines (eye drops)	485 (8.2)	261 (37.3)	<.001	175 (52.2)	34 (17.2)	15 (23.4)	12 (34.3)	<.001	12 (38.7)
Antihistamines (oral)	563 (9.5)	162 (23.1)	<.001	35 (10.4)	85 (42.9)	28 (43.8)	11 (31.4)	<.001	10 (32.3)

Data presented as mean (standard deviation) for age, and n (%) for other characteristics.

[a]Received any eye drops of fluorometholone, betamethasone, dexamethasone, or hydrocortisone, but no other ophthalmic corticosteroids.

[b]Received any ointments of prednisolone or dexamethasone, but no other ophthalmic corticosteroids.

TABLE 7. Neonatal Adverse Outcomes According to Exposure To Ophthalmic Corticosteroids

		Exposed to Corticosteroid Eye Drops				Exposed to Corticosteroid Ointment	
	Unexposed	Any	Fluorometholone 0.1% alone	Betamethasone 0.1% alone	Dexamethasone 0.1% alone	Any	Prednisolone alone
	n = 5,949	n = 700	n = 335	n = 198	n = 64	n = 35	n = 31
Congenital anomaly	330 (5.5)	34 (4.9)	15 (4.5)	9 (4.5)	4 (6.2)	2 (5.7)	2 (6.5)
Preterm birth	203 (3.4)	27 (3.9)	11 (3.3)	10 (5.1)	3 (4.7)	0 (0.0)	0 (0.0)
Low birthweight	352 (5.9)	49 (7.0)	26 (7.8)	11 (5.6)	5 (7.8)	0 (0.0	0 (0.0)
Composite outcome	697 (11.7)	82 (11.7)	39 (11.6)	22 (11.1)	8 (12.5)	2 (5.7)	2 (6.5)

Data presented as n (%).

without exposure to corticosteroid ointments was similar, except there were no significant differences in the proportions of asthma (Table 6).

Adverse neonatal outcomes of babies born to women with and without exposure to ophthalmic corticosteroids are shown in Table 7. The proportions of congenital anomalies were 5.5% and 4.9% in those unexposed and exposed to any corticosteroid eyedrops, respectively; proportions of preterm birth were 3.4% and 3.9%, respectively; proportions of low birthweight were 5.9% and 7.0%, respectively; and proportions of the composite outcomes were 11.7% and 11.7%, respectively.

The results of PS adjustment analysis for adverse neonatal outcomes are shown in Table 8. Use of ophthalmic corticosteroids during the first trimester was not significantly associated with an increased frequency of congenital anomalies (adjusted odds ratio [aOR], 0.78; 95% confidence interval [CI], 0.54-1.14; $P = .20$), preterm birth (aOR, 1.23; CI, 0.80-1.88; $P = .35$), low birthweight (aOR, 1.17; CI 0.84-1.61; $P = .35$), or composite outcome (aOR, 0.95; CI,0.73-1.22; $P = .68$). Similarly, use of ophthalmic corticosteroids was not significantly associated with an increased frequency of adverse neonatal outcomes in any comparison of unexposed versus fluorometholone 0.1%, betamethasone 0.1%, or dexamethasone 0.1%, any corticosteroid ointments, or prednisolone ointment.

DISCUSSION

ANALYSIS OF A LARGE CLAIM DATABASE DEMONSTRATED no significant differences in adverse neonatal outcomes (congenital anomalies, preterm birth, low birthweight, and composite outcome) between babies born to women with and those born to women without exposure to ophthalmic corticosteroids, with adjustment for various confounders.

The overall proportion of individuals with AC in our study was 10%, which was within the range reported in previous studies.[1,2] Of the eligible women with AC, only 13% had used ophthalmic corticosteroids during the first trimester. That low proportion might have been because doctors tend to avoid prescribing ophthalmic corticosteroids to pregnant women because of the possible adverse effects on the mothers and fetuses. Generally, treatment for AC is not essential in pregnant women because it is rarely a vision-threatening disease, such as glaucoma, age-related macular degeneration, and uveitis. However, AC can significantly reduce various aspects of quality of life. Indeed, quality of life scores were lower in patients with AC than in controls, using the EQ-5D Health Questionnaire, the National Eye Institute Visual Functioning Questionnaire 25, and the Rhinoconjunctivitis Quality of Life Questionnaire.[5] It is therefore important to establish the safety of ophthalmic corticosteroids in pregnant women, to facilitate their use, and to improve the patient's quality of life. The current results support this situation.

In the present study, congenital anomalies occurred in 5.4% of all eligible women, comparable to previous reports (3.0%-8.6%).[18,27,28] Preterm births occurred in 3.4% of the women, which was similar to the incidence in a previous Japanese study (4.8%).[29] Low birthweight occurred in 6.0% of women. A previous population-based study in Japan reported low-birthweight rates of 4.5% in 1979 and 8.3% in 2010, with a significant increase over time,[30] suggesting that the current low-birthweight rate would be >8.3%, in line with the rate of 6.0% for the period from 2005 to 2018 in the present study. Based on those findings, the authors considered this dataset was valid.

The most frequently and second-most frequently prescribed medications in the current study were fluorometholone 0.1% and betamethasone 0.1%, respectively, which were also the most commonly prescribed medications in a previous study.[31] In terms of concentration, the highest concentration of 0.1% was prescribed more frequently than lower concentrations (fluorometholone 0.05% and 0.02%; betamethasone 0.01%) in the present study. Considering that corticosteroids are generally used for AC in patients resistant to antihistamines,[32] eye drops

TABLE 8. Association Between Use of Ophthalmic Corticosteroids and Adverse Neonatal Outcomes after Propensity Score Adjustment

	Unexposed	Exposed to Corticosteroid Eye Drops								Exposed to Corticosteroid Ointment			
		Any		Fluorometholone 0.1% alone		Betamethasone 0.1% alone		Dexamethasone 0.1% alone		Any		Prednisolone alone	
	5,949	700	*P*	335	*P*	198	*P*	64	*P*	35	*P*	31	*P*
Congenital anomaly	Ref	0.78 (0.54-1.14)	.20	0.73 (0.42-1.27)	.26	0.75 (0.38-1.49)	.41	0.84 (0.29-2.44)	.75	1.04 (0.25-4.36)	.96	1.18 (0.28-4.99)	.82
Preterm birth	Ref	1.23 (0.80-1.88)	.35	1.1 (0.57-2.11)	.77	1.64 (0.84-3.2)	.15	1.53 (0.47-5.00)	.48	[a]	-	-	-
Low birthweight	Ref	1.17 (0.84-1.61)	.35	1.17 (0.75-1.83)	.49	0.95 (0.51-1.79)	.88	1.5 (0.59-3.8)	.40	-	-	-	-
Composite outcome	Ref	0.95 (0.73-1.22)	.68	0.91 (0.63-1.32)	.63	0.91 (0.58-1.44)	.69	0.98 (0.46-2.09)	.96	0.52 (0.12-2.17)	.37	0.58 (0.14-2.46)	.46

Data are adjusted odds ratios with 95% confidence intervals.
[a]No outcomes.

with high concentrations of corticosteroids may be required. However, there were no significant associations between high-concentration corticosteroid eye drops and adverse neonatal events in the present study, suggesting that lower concentrations of corticosteroids would also have no adverse outcomes.

In terms of pharmacokinetics, approximately one-third of the total amount of the administered corticosteroid eye drops will be distributed systemically in 30 min.[33] In a prior study, the concentration of corticosteroids increased in various organs, including the liver, after application of corticosteroid eye drops in rabbits.[34] Furthermore, the concentration of endogenous steroids in humans decreased after the application of corticosteroid eye drops (dexamethasone, 0.01% every hour,[35] and dexamethasone, 0.1% 8 times a day[36]), indicating that corticosteroid eye drops may cause adrenal suppression. This suggests that corticosteroid eye drops may have the potential to cause adverse neonatal outcomes.

However, none of the ophthalmic corticosteroids administered in the current study were associated with adverse neonatal outcomes. A recent review of published clinical studies found little evidence to indicate that corticosteroid use in the first trimester induced preterm birth or low birthweights.[15] Although the authors suggested that anomalies, especially cleft lip, may be associated with corticosteroid use, the data were conflicting, and the results of some previous studies might have been biased by the presence of underlying maternal diseases, such as autoimmune diseases. No studies since 2003 have indicated any significant association between corticosteroid use and congenital anomalies, including the largest study to date from the National Birth Defects Prevention Study.[15] Furthermore, these prior studies focused on oral or systemic rather than ophthalmic corticosteroids. Given that the peak serum concentration of betamethasone is much lower following ophthalmic compared with oral administration (0.46 ng/ml and 5.0 ng/ml, respectively),[37,38] ophthalmic corticosteroids would be expected to have much less influence on the fetus. The absorption ratio of ointments is even lower than that of eye drops.[39,40] Overall, these studies suggest that ophthalmic corticosteroids are likely to have little influence on the fetus, adding biological plausibility to the current results.

This study had several limitations. First, it could not be determined if the women actually used the ophthalmic corticosteroids prescribed, leading to a potential underestimation of the risks. However, the use of prescription data has the advantage of eliminating recall bias associated with self-reported data. Second, information could not be obtained for the daily frequency and duration of treatment from the database and any dose-dependent effects were unable to be analyzed. Third, the sample size might not have been large enough to draw firm conclusions. Fourth, it is possible that some adverse neonatal outcomes were not detected. Details of the mothers' prenatal care and specific information regarding the neonates' examinations were not

available in the database. Fifth, perinatal care practices in Japan may limit the generalizability of the findings: the recommended number of prenatal visits is relatively high,[41] and almost all pregnant women deliver at medical facilities.[42] These factors might have influenced the frequency of neonatal outcomes.

However, given that randomized controlled trials cannot be conducted for ethical reasons, these results provide valuable practical data. Based on a previous study showing that corticosteroids were prescribed for AC more frequently than antihistamines in a clinical setting (41% and 29%, respectively),[43] our results may help many pregnant women with AC.

In conclusion, the use of ophthalmic corticosteroids during the first trimester was not associated with adverse neonatal outcomes (congenital anomalies, preterm birth, low birthweight, and composite outcome) according to PS adjustment analysis. These results will be valuable for ophthalmologists prescribing ophthalmic corticosteroids to pregnant women with AC.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

Funding/Support: Supported by Ministry of Health, Labour and Welfare, Japan grants H30-Policy-Designated-004 and H29-ICT-General-004 and Ministry of Education, Culture, Sports, Science and Technology, Japan grant 17H04141. The sponsor or funding organization had no role in the design or conduct of this research.

Financial Disclosures: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Leonardi A, Castegnaro A, Valerio ALG, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol* 2015;15:482–488.
2. Brożek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466–476.
3. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988–1994. *J Allergy Clin Immunol* 2010;126:778–783.
4. Petricek I, Prost M, Popova A. The differential diagnosis of red eye: a survey of medical practitioners from eastern europe and the middle east. *Ophthalmologica* 2006;220:229–237.
5. Smith AF, Pitt AD, Rodruiguez AE, et al. The economic and quality of life impact of seasonal allergic conjunctivitis in a Spanish setting. *Ophthalmic Epidemiol* 2005;12:233–242.
6. Pitt AD, Smith AF, Lindsell L, Voon LW, Rose PW, Bron AJ. Economic and quality-of-life impact of seasonal allergic conjunctivitis in Oxfordshire. *Ophthalmic Epidemiol* 2004;11:17–33.
7. Vaajanen A, Vapaatalo H. A single drop in the eye—effects on the whole body? *Open Ophthalmol J* 2017;11:305–314.
8. Gur C, Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. *Reprod Toxicol* 2004;18:93–101.
9. Chakravarty EF, Colón I, Langen ES, et al. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. *Am J Obstet Gynecol* 2005;192:1897–1904.
10. Al Arfaj A, Khalil N. Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. *Lupus* 2010;19(14):1665–1673.
11. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;62:385–392.
12. Hviid A, Molgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *Can Med Assoc J* 2011;183:796–804.
13. Nørgård B, Pedersen L, Christensen LA, Sørensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish Nationwide Cohort Study. *Am J Gastroenterol* 2007;102:1406–1413.
14. Skuladottir H, Wilcox AJ, Ma C, et al. Corticosteroid use and risk of orofacial clefts: corticosteroid use and orofacial clefts risk. *Birth Defects Res A Clin Mol Teratol* 2014;100:499–506.
15. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. *Rheum Dis Clin N Am* 2017;43:489–502.
16. Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. *J Epidemiol* 2010;20:413–419.
17. Spong CY. Defining "term" pregnancy: recommendations from the defining "term" pregnancy workgroup. *JAMA* 2013;309:2445–2446.
18. Bérard A, Sheehy O, Zhao J-P, et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *Can Med Assoc J* 2019;191:E179–E187.
19. Sheehy O, Zhao J-P, Bérard A. Association between incident exposure to benzodiazepines in early pregnancy and risk of spontaneous abortion. *JAMA Psychiatry* 2019;76:948.
20. Bérard A, Sheehy O, Kurzinger M-L, Juhaeri J. Intranasal triamcinolone use during pregnancy and the risk of adverse pregnancy outcomes. *J Allergy Clin Immunol* 2016;138:97–104.
21. Rom AL, Wu CS, Olsen J, et al. Fetal growth and preterm birth in children exposed to maternal or paternal rheumatoid arthritis: a Nationwide Cohort Study. *Arthritis Rheumatol* 2014;66:3265–3273.
22. Mitchell K, Kaul M, Clowse M. The management of rheumatic diseases in pregnancy. *Scand J Rheumatol* 2010;39:99–108.

23. Malone DC, Lawson KA, Smith DH, Arrighi HM, Battista C. A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99:6.
24. Goldenberg RL, Culhane JF, Iams JD, Romero R. Preterm birth 1 epidemiology and causes of preterm birth. *Lancet* 2008;371:75–84.
25. Michihata N, Shigemi D, Sasabuchi Y, Matsui H, Jo T, Yasunaga H. Safety and effectiveness of Japanese herbal Kampo medicines for treatment of hyperemesis gravidarum. *Int J Gynecol Obstet* 2019;145:182–186.
26. Cepeda MS. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol* 2003;158:280–287.
27. Egbe AC. Birth defects in the newborn population: race and ethnicity. *Pediatr Neonatol* 2015;56:183–188.
28. Brent RL, Beckman DA. Environmental teratogens. *Bull N Acad Med* 1990;66:41.
29. Sakata S, Konishi S, Ng CFS, Watanabe C. Preterm birth rates in Japan from 1979 to 2014: analysis of national vital statistics: preterm birth rates in japan. *J Obstet Gynaecol Res* 2018;44:390–396.
30. Takemoto Y, Ota E, Yoneoka D, Mori R, Takeda S. Japanese secular trends in birthweight and the prevalence of low birthweight infants during the last three decades: a population-based study. *Sci Rep* 2016;6:31396.
31. Holland EJ, Fingeret M, Mah FS. Use of topical steroids in conjunctivitis: a review of the evidence. *Cornea* 2019;38:1062–1067.
32. American Academy of Ophthalmology Cornea/External Disease Preferred Practice Pattern Panel. Preferred practice pattern guidelines: conjunctivitis. Available at: https://www.aao.org/preferred–practice–pattern/conjunctivitis-ppp-2018. Accessed March 5, 2020.
33. Wine NA, Gognall AG, Basu PK. The ocular uptake of subconjunctivally injected C14 hydrocortisone. 1. Time and major route of penetration in a normal eye. *Am J Ophthalmol* 1964;58:362–366.
34. Rosenblum C, Dengler RE Jr, Geoffroy RF. Ocular absorption of dexamethasone phosphate disodium by the rabbit. *Arch Ophthalmol* 1967;77:234–237.
35. Burch PG, Migeon CJ. Systemic absorption of topical steroids. *Arch Ophthalmol* 1968;79:174–176.
36. Krupin T, Mandell AI, Podos SM, Becker B. Topical corticosteroid therapy and pituitary-adrenal function. *Arch Ophthalmol* 1976;94:919–920.
37. Baba S, Mishima H, Okimoto M, Miyachi Y. Plasma steroid levels and clinical effects after topical application of betamethasone. *Graefes Arch Clin Exp Ophthalmol* 1983;220:209–214.
38. Kubota K, Lo E, Huttinot G, Andersen P, Maibach H. Plasma concentrations of betamethasone after topical application of betamethasone 17-valerate: comparison with oral administration. *Br J Clin Pharmacol* 1994;37:86–88.
39. Kupferman A, Pratt MV, Suckewer K, Leibowitz HM. Topically applied steroids in corneal disease. 3. the role of drug derivative in stromal absorption of dexamethasone. *Arch Ophthalmol (Chicago IL) 1960* 1974;91:373–376.
40. McGhee CN. Pharmacokinetics of ophthalmic corticosteroids. *Br J Ophthalmol* 1992;76(11):681–684.
41. Japan Society of Obstetrics and Gynecology. Guidelines for obstetrical practice in Japan 2017. https://minds.jcqhc.or.jp/docs/minds/Obstetrical-practice/Obstetrical-practice.pdf. Accessed October 7, 2020.
42. Statistics Bureau, Ministry of Internal Affairs and Communication of Japan.. Vital statistics of Japan (2018). Available at: https://www.e-stat.go.jp/dbview?sid=0003411600. Accessed May 24, 2020.
43. Leonardi A, Piliego F, Castegnaro A, et al. Allergic conjunctivitis: a cross-sectional study. *Clin Exp Allergy* 2015;45:1118–1125.