

Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort



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Background: The Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy (EXPECT) pregnancy registry was a prospective observational study established in 2006 to evaluate perinatal outcomes in pregnant women exposed to omalizumab and their infants.

Objective: This analysis compares EXPECT outcomes with those from a disease-matched population of pregnant women

not treated with omalizumab. Data from a substudy of platelet counts among newborns are also presented.

Methods: The EXPECT study enrolled 250 women with asthma exposed to omalizumab during pregnancy. The disease-matched external comparator cohort of women with moderate-to-severe asthma ($n = 1153$), termed the Quebec External Comparator Cohort (QECC), was created by using data from health care databases in Quebec, Canada. Outcome estimates were age adjusted based on the maternal age distribution of the EXPECT study.

Results: Among singleton infants in the EXPECT study, the prevalence of major congenital anomalies was 8.1%, which was similar to the 8.9% seen in the QECC. In the EXPECT study 99.1% of pregnancies resulted in live births, which was similar to 99.3% in the QECC. Premature birth was identified in 15.0% of EXPECT infants and 11.3% in the QECC. Small for gestational age was identified in 9.7% of EXPECT infants and 15.8% in the QECC.

Conclusion: There was no evidence of an increased risk of major congenital anomalies among pregnant women exposed to omalizumab compared with a disease-matched unexposed cohort. Given the observational nature of this registry, however, an absence of increased risk with omalizumab cannot be definitively established. (*J Allergy Clin Immunol* 2020;145:528-36.)

Key words: Omalizumab, pregnancy, moderate to severe asthma, congenital anomalies

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Uncontrolled or severe asthma can increase the risk of perinatal mortality, prematurity, low birth weight, and reduced fetal growth; therefore pregnant women with asthma are advised to maintain any asthma treatment in use at the time of conception and throughout pregnancy.¹⁻³ However, there is conflicting evidence on asthma, asthma medication use, and risk of congenital anomalies. Although one study found no increased risk of congenital anomalies with exposure to high-dose systemic corticosteroids, other studies have documented a small increase in the risk of cleft palate with exposure to high-dose systemic corticosteroids and an increased risk of overall congenital malformations after exposure to high-dose inhaled corticosteroids (ICSs).⁴⁻⁶ Another study found that severe asthma exacerbations during pregnancy significantly increased the risk of congenital malformations compared with moderate or no exacerbations.⁷ A proposed mechanism for this relationship is

Abbreviations used

BMI:	Body mass index
EXPECT:	Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy
HCP:	Health care provider
ICS:	Inhaled corticosteroid
QECC:	Quebec External Comparator Cohort
RAMQ:	Régie de l'assurance maladie du Québec
SGA:	Small for gestational age

that asthma exacerbations provoke maternal hypoxia and other blood gas abnormalities that can influence fetal development.¹

Treatment for moderate-to-severe asthma has evolved over the last decade to include biologics, such as omalizumab. Omalizumab is a recombinant anti-IgE mAb licensed in the United States as an add-on therapy for the treatment of patients aged 6 years or more with moderate-to-severe persistent allergic asthma that is inadequately controlled with ICSs.⁸ In the European Union omalizumab is approved for patients 6 years of age and older with severe persistent allergic asthma that is inadequately controlled with ICSs and long-acting β_2 -agonists.⁹ Preclinical simian studies found no association between omalizumab and teratogenicity, embryotoxicity, or maternal toxicity.⁸ In these same studies omalizumab administration throughout late gestation, delivery, and nursing elicited no adverse effects on fetal or neonatal growth.⁸ Omalizumab was shown to decrease blood platelet levels when administered at suprapharmacologic doses in several species of nonhuman primates.

The Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy (EXPECT) was a postmarketing commitment to the US Food and Drug Administration to assess outcomes in pregnant women and their offspring who were exposed to omalizumab. The US Food and Drug Administration also requested a substudy of neonatal platelet counts because of the findings of decreased blood platelet counts in nonhuman primates.

Previously published interim data from the EXPECT pregnancy registry found that the proportions of infants with major congenital anomalies, prematurity, low birth weight, and small for gestational age (SGA) status were consistent with findings from published studies of women with severe asthma.¹⁰ This publication compares the final data from the EXPECT registry with findings from a disease-matched comparator population of pregnant women with moderate-to-severe asthma who were not treated with omalizumab. Data on newborn platelet counts from the EXPECT Neonatal Platelet Count Substudy are also presented.

METHODS

Study design

The EXPECT study was an observational, exposure registration, prospective cohort study conducted in the United States. Enrollment was voluntary and began in October 2006 and ended in December 2017; follow-up continued until January 2018. Women were eligible to enroll if they were currently pregnant and received 1 or more doses of omalizumab at any time during pregnancy or during the 8 weeks before conception (a window selected to reflect omalizumab's half-life of 26 days).⁸ Data analyses excluded women with abnormal findings on pre-enrollment prenatal diagnostic testing ($n = 11$),

women without asthma who were treated with omalizumab for chronic idiopathic urticaria ($n = 37$), and women with missing data on omalizumab exposure ($n = 2$) and excluded subsequent pregnancies after the initial enrollment pregnancies ($n = 9$). Thus 250 pregnant women with asthma who prospectively enrolled were included in the analysis. The sample size was chosen to provide statistical power to rule out a 2- to 3-fold increase in the risk of congenital malformations compared with various estimates of background prevalence in the United States (3% to 6%) reported from birth defect surveillance systems and studies in women with asthma.^{5,11,12} Follow-up and data collection were completed in December 2017.

The study was approved by the Western Institutional Review Board (Puyallup, Washington). All women provided informed consent to participate, and medical release forms were obtained to allow health care providers (HCPs) to report data to the registry.

Data collection

Data were collected by telephone from participants and their HCPs at enrollment, each pregnancy trimester, and delivery or pregnancy termination. Infant outcome data were collected at birth and up to 18 months of age. Information collected on maternal demographics and disease status included maternal age, body mass index (BMI), smoking status, prenatal testing, asthma severity (based on subjective assessment by omalizumab prescriber), omalizumab exposure, and other medication or substance use. Information collected on outcome measures included fetal death/stillbirth (≥ 20 weeks' gestation), gestational age at birth, infant birth weight, congenital anomalies (defined below), infant thrombocytopenia (captured as a targeted adverse event and defined as any sign or symptom of low platelet count in the neonate), and adverse events.

An external advisory committee composed of specialists in teratology, pharmacoepidemiology, maternal-fetal medicine, pediatrics, and asthma/allergy reviewed registry data semiannually. Additionally, all reports of potential congenital anomalies were reviewed by an independent external geneticist and categorized by using a system derived from that of the Metropolitan Atlanta Congenital Defects Program, in which major defects are defined as anomalies that have either cosmetic or functional significance to the infant and minor defects are defined as common deviations from normal structure or function that are unlikely to require medical or surgical intervention.¹³

External comparator

Identifying a comparator for which information on asthma severity is available is important to place the results of the EXPECT study into context, given that asthma severity and associated treatments can be related to the risk for adverse pregnancy outcomes. Thus findings for relevant mother and infant subgroups were compared with age-adjusted frequencies in a disease-matched external cohort of women with moderate-to-severe asthma unexposed to omalizumab during pregnancy. This comparator, the Quebec External Comparator Cohort (QECC), was generated from the Quebec Asthma and Pregnancy Database, which was built by linking 2 health care databases in the Canadian province of Quebec.

One database, the Régie de l'assurance maladie du Québec (RAMQ), contains data on medical services and prescription medications dispensed in community pharmacies for residents of Quebec covered by the RAMQ Public Drug Insurance Plan (approximately 42% of the residents of Quebec). The other, the Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière database, contains data on acute care hospitalizations and covers all residents of Quebec. These Quebec health administrative databases were chosen for developing the QECC because they provide a large sample size and because diagnoses of congenital malformations have been formally validated in previous studies.^{14,15} The Quebec databases also contained data for determination of maternal asthma severity, which allowed for selection of a cohort with a background risk for adverse pregnancy outcomes expected to be similar to that of the EXPECT subcohort.

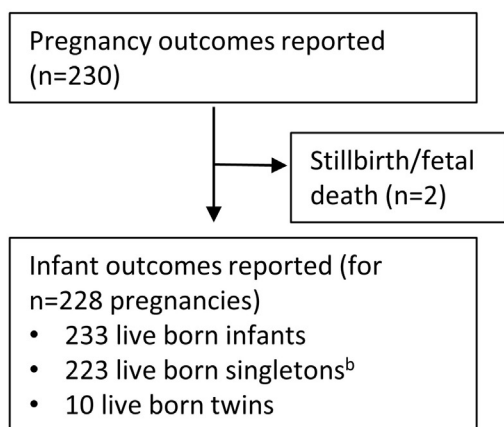
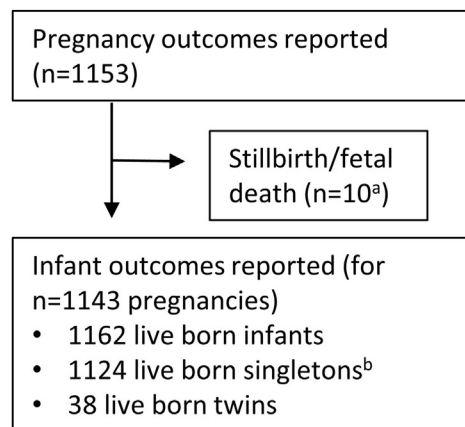
Women were included in the QECC if their most recent pregnancy was recorded between January 1, 1990, and March 31, 2009; they were covered by the RAMQ Drug Insurance Plan for at least 3 months before and during

EXPECT Pregnancy Registry

Prospectively enrolled women with asthma (n= 250)

Excluded to form EXPECT subcohort

- Mild asthma (n= 7)
- Spontaneous abortion (n= 11)
- Elective termination (n= 1)
- Pregnancy outcome missing (n= 1)

EXPECT Subcohort**Quebec External Comparator Cohort (QECC)**

^a8 singleton stillbirths and 2 twin pregnancies with 1 stillbirth and 1 live birth each

^bSubgroup for reporting major congenital anomalies

FIG 1. Study populations.

pregnancy; they had a diagnosis of asthma recorded at least once in the 2 years before delivery; they had moderate or severe asthma; they received ICS treatment in the first trimester of pregnancy; and they had no omalizumab prescription fills during pregnancy or in the 8 weeks before conception. Pregnancies terminated before 20 weeks' gestation are not recorded in the Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière database and therefore were not included in the QECC.

A comparator-specific EXPECT subcohort, referred to below as the EXPECT subcohort, was formed to align with the QECC by excluding pregnancies that terminated before 20 weeks' gestation and women with mild asthma severity. Fig 1 displays how the study populations were formed and the numbers of pregnancies and infants included in each group. Table I compares data available for the EXPECT study and the QECC on identification and classification of congenital anomalies, asthma severity, other outcomes, and potential confounders.

Data analysis

Comparison between the EXPECT study and the QECC was intended to be descriptive, without formal statistical comparisons. Outcomes from the QECC were age standardized by using the EXPECT study's maternal age distribution (in 5-year increments) as the reference population. Demographic and clinical characteristics were summarized descriptively with percentages for categorical variables and with means and SDs or medians and ranges for continuous variables. The frequency of pregnancy and infant outcomes, including live births, stillbirths, premature births, low birth weight, SGA, and major congenital anomalies, were summarized as proportions with 2-sided 95% CIs for binomial proportions without adjustment for multiplicity or as

means with SDs or medians with ranges. The denominator for pregnancy outcomes was the number of women, and for infant incomes, the denominator for pregnancy outcomes was number of live births with nonmissing values for the outcome; any exceptions are noted. A *post hoc* analysis was conducted to examine the potential association between obesity and oral corticosteroid use on prematurity and low birth weight.

Neonatal Platelet Substudy methods

The objective of the Neonatal Platelet Substudy was to evaluate neonatal platelet counts in infants exposed to omalizumab during pregnancy. This was a single-arm study with no comparator. Any infant whose mother was enrolled in the EXPECT pregnancy registry was eligible to participate in the substudy. Enrollment was voluntary. Among infants for whom a parent provided informed consent for the substudy (n = 72), a single blood sample was obtained from 51 infants and submitted to a central laboratory for measurement of platelet counts.

RESULTS

The EXPECT registry prospectively enrolled 250 pregnant women with asthma, one of whom was lost to follow-up before pregnancy outcome was known (Fig 1). The EXPECT subcohort included in this comparison was composed of 230 pregnant women. There were 2 stillbirths/fetal deaths and 233 live-born infants, including 223 live-born singletons and 5 live-born twin pairs. The QECC was composed of 1153 women. There were

TABLE I. Comparison of data source, definition, and classification for selected variables in the EXPECT study and the QECC

	EXPECT study	QECC
Definition of maternal asthma severity	Subjective assessment by omalizumab prescribers	Asthma severity defined according to the American asthma guidelines (NHLBI guidelines)¹ Moderate asthma, women who used any of the following: ● LABAs (salmeterol or formoterol) plus low-dose ICSs (fluticasone, beclomethasone, triamcinolone, flunisolide, budesonide, or ciclesonide) ● Medium-dose ICS monotherapy ● Low-dose ICS plus LTRA ● Theophylline during the first trimester of pregnancy Severe asthma, women who used any of the following: ● High-dose ICS monotherapy ● Medium- to high-dose ICS plus either LABA, long-acting muscarinic antagonist, LTRA, or theophylline ● Daily oral corticosteroids with or without any controller medication during the first trimester
Data sources for asthma medications, including omalizumab	Telephone interviews with women and omalizumab prescribers	RAMQ Prescription Medications file contains data on all medications dispensed to participants in the RAMQ Drug Insurance Plan
Data sources for live births and stillbirths (fetal loss at or after 20 weeks' gestation)	Telephone interviews with women and health care providers	Recorded in the RAMQ or MED-ECHO databases, with live births defined by ICD-9 codes 650.9 or 640-676 or ICD-10 code Z37 and stillbirths defined by ICD-9 codes V27.1, V27.3, V27.4, V27.6, V27.7, V32, V35, V36, or 656.4 or ICD-10 codes O36.4, Z37.1, Z37.3, Z37.4, Z37.6, or Z37.7
Data sources for congenital anomalies and classification system	Telephone interviews with women and health care providers Classified according to Scheuerle and Tilson ¹³ Derived from MACDP	Recorded in the RAMQ or MED-ECHO databases, with diagnostic codes specific to congenital malformations (ICD-9 code 740-759 or ICD-10 code Q01-Q99) In some cases "major" classification was determined by having a hospitalization
Data sources for birth weight and gestational age of infant	Telephone interviews with women and health care providers	Recorded in the MED-ECHO database (delivery record)
Potential confounders: smoking, alcohol use, BMI	Telephone interviews with women and health care providers	Not available
Data source and definition of thrombocytopenia*	Telephone interviews and health care providers Defined as a targeted adverse event with any sign or symptom of low platelet counts in neonates	Recorded in the RAMQ or MED-ECHO databases defined by ICD-9 code 776.1 or ICD-10 (code 61.0)

ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; LABA, Long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; MACDP, Metropolitan Atlanta Congenital Defects Program; MED-ECHO, Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière; NHLBI, National Heart, Lung, and Blood Institute.

*Note: The definition of thrombocytopenia in the neonatal platelet study was based on platelet count.

10 stillbirths/fetal deaths and 1162 live-born infants with outcome data, including 1124 live-born singletons and 19 live-born twin pairs.

The median gestational age at enrollment in the EXPECT subcohort was 11.0 weeks (range, 3.9-39.6 weeks). Almost all participants (98.3%) were exposed to omalizumab during the first trimester of pregnancy or during the 8 weeks before conception, and 83.0% of participants were exposed to omalizumab during all 3 trimesters of their pregnancy (Table II). The median duration of pregnancy exposure was 8.8 months (range, 1.0-9.9 months). The

2 most commonly administered doses during pregnancy were 300 mg (37.0%) and 375 mg (21.8%), and more than half of the women (52.8%) received omalizumab every 2 weeks.

Maternal demographics and clinical characteristics

Women in the EXPECT subcohort were older than those in the QECC, with a median age of 30.0 versus 27.7 years, respectively; percentages of subjects aged less than 35 years were 74.8% and 85.7%, respectively (Table III). The proportion of women in the

TABLE II. Omalizumab exposure at enrollment, during pregnancy, and after delivery (EXPECT subcohort)*

Omalizumab exposure during pregnancy	Total (n = 230)
Exposure duration (mo)	
No.	230
Median (range)	8.8 (1.0-9.9)
Dose level†	
No.	216
150 mg	40 (18.5%)
225 mg	30 (13.9%)
300 mg	80 (37.0%)
375 mg	47 (21.8%)
Other	19 (8.8%)
Dosing interval (week)‡	
No.	216
Every 2 wk	114 (52.8%)
Every 4 wk	97 (44.9%)
Other	5 (2.3%)
Earliest exposure	
No.	230
First trimester‡	226 (98.3%)
Second trimester	4 (1.7%)
Third trimester	0 (0.0%)
Overall exposure	
Any first trimester‡	226 (98.3%)
Any second trimester	199 (86.5%)
Any third trimester	197 (85.7%)
All trimesters	191 (83.0%)

*This EXPECT subcohort excludes pregnancies that terminated before 20 weeks' gestation and women with mild asthma severity, which are not available in the Quebec database.

†Summarized by using data collected at first successful contact with the prescriber.

‡Includes exposure within 8 weeks before conception.

EXPECT subcohort who were obese (BMI >30 kg/m² before pregnancy) was 46.7%, and the proportion who reported cigarette smoking was 7.4%. Data on obesity, BMI, and smoking were not available in the QECC.

Women in the EXPECT subcohort were more likely to have severe asthma than those in the QECC. The percentage of women classified as having severe asthma in the EXPECT subcohort was 64.9% compared with 21.2% in the QECC; for moderate asthma, this was 35.1% in the EXPECT subcohort and 78.8% in the QECC. Differences in the definitions of asthma severity are noted in Table I.

Based on the study definitions of moderate and severe asthma in the QECC, all women in the QECC were taking ICSs during pregnancy. An additional 46.2% were also taking long-acting β_2 -agonists. In comparison, 81.3% of women in the EXPECT subcohort had documented ICS use during pregnancy. Among women in the QECC, 22.8% received 1 or more prescription fills for any oral corticosteroid during pregnancy, and among women in the EXPECT subcohort, 23.7% took any oral corticosteroid at least once during pregnancy, as reported by the woman or her HCP.

Pregnancy and infant outcomes

In the EXPECT subcohort and the QECC, rates of live births were similar (99.1% and 99.3%, respectively; Table IV).^{16,17} Among live-born infants, the mean birth weight for singletons was 3.2 kg in both the EXPECT subcohort and the QECC. Among all live-born infants in the EXPECT subcohort, 13.7% had low birth weight compared with 9.8% for the QECC. Among full-term singletons, the proportions were

TABLE III. Maternal demographics and clinical characteristics (EXPECT subcohort and the QECC)

	EXPECT subcohort* (n = 230)	QECC (n = 1153)
Age (y)		
Median (range)	30.0 (16-45)†	27.7 (15.3-44.6)‡
% <35 y	74.8%†	85.7%‡
Obesity	46.7%§	NA
Smoking	7.4%	NA
Asthma medications during pregnancy		
ICSs	81.3%	100.0%¶
Leukotriene receptor antagonists	49.6%	7.8%
Oral corticosteroids	23.7%	22.8%

*This EXPECT subcohort excludes pregnancies that terminated before 20 weeks' gestation and women with mild asthma severity, which are not available in the Quebec database.

†Maternal age at enrollment.

‡Maternal age at delivery.

§Obesity is defined as BMI of greater than 30 mg/kg² before pregnancy.

||Data not available in the QECC.

¶Per-study definition of moderate and severe asthma in the QECC. All women in the QECC were taking ICSs during pregnancy. An additional 46.2% were also taking long-acting β_2 -agonists.

similar at 2.7% (EXPECT subcohort) and 2.9% (QECC). Among all live-born infants in the EXPECT subcohort, 15.0% were premature compared with 11.3% of QECC infants.

A *post hoc* analysis was conducted to examine the potential association between prepregnancy obesity and oral corticosteroid use on prematurity and low birth weight. Within the EXPECT subcohort, the prevalence of premature birth was 17.5% among obese women compared with 11.0% among nonobese women. Among women who did not take an oral corticosteroid, the prevalence of premature birth was similar between the EXPECT subcohort (9.6%) and the QECC (9.8%). Among women who took any oral corticosteroid at any time during pregnancy, the prevalence of premature birth was 32.7% in the EXPECT subcohort compared with 16.2% for the QECC (Table IV). The prevalence of low-birth-weight births among women who did not take an oral corticosteroid was 12.3% in the EXPECT subcohort and 8.7% in the QECC, and among women who took any oral corticosteroid, it was 18.2% (EXPECT subcohort) and 13.7% (QECC).

In the EXPECT subcohort 9.7% of infants were classified as being SGA compared with 15.8% for the QECC. Among live singletons in the EXPECT subcohort, thrombocytopenia was spontaneously reported as an adverse event in 1 infant (0.4% [1/230]). In the QECC 0.6% (7/1124) of live singletons had a diagnosis of thrombocytopenia recorded at birth or in the month after delivery.

Congenital anomalies

Major congenital anomalies were reported in 8.1% of live singleton infants in the EXPECT subcohort and 8.9% in the QECC (Table V). In preliminary analyses, in both the EXPECT subcohort and the QECC, the prevalence of major congenital anomalies among infants born to women with severe asthma was not greater than the prevalence among infants born to women with moderate asthma. Therefore no further analyses stratified by asthma severity (severe vs moderate) were conducted.

The organ system with the greatest frequency of major anomalies in the EXPECT subcohort was the eye, ear, face, and neck system (2.2% [n = 5]); all of these cases were torticollis. In

TABLE IV. Pregnancy and infant outcomes (excluding congenital anomalies) in the EXPECT subcohort and the QECC

	EXPECT subcohort*	QECC†
Pregnancy outcomes	n = 230	n = 1153
Live births (% of pregnancies [95% CI])	99.1% (96.9% to 99.9%)	99.3% (92.9% to 100.0%)‡
Fetal death/stillbirths‡ (% of pregnancies [95% CI])	0.9% (0.1% to 3.1%)	0.9% (0.3% to 1.5%)‡
Live-born infant outcomes§	n = 233	n = 1162
Birth weight (kg), mean ± SD		
All infants	3.2 ± 0.6	3.2 ± 0.6
Singletons	3.2 ± 0.6	3.2 ± 0.3
Twins	2.4 ± 0.4	2.0 ± 0.3
Low birth weight (% of infants [95% CI])¶		
All infants	13.7% (9.5% to 18.9%)	9.8% (7.9% to 11.8%)
All singletons, including premature births	11.6% (7.6% to 16.6%)	8.3% (6.5% to 10.2%)
All full-term infants	4.7% (2.2% to 8.8%)	2.9% (1.8% to 4.0%)
Full-term singletons	2.7% (0.9% to 6.1%)	2.9% (1.8% to 4.0%)
Oral corticosteroid use#		
Yes	18.2% (9.1% to 30.9%)	13.7% (8.8% to 18.6%)
No	12.3% (7.8% to 18.2%)	8.7% (6.6% to 10.8%)
SGA (% of infants [95% CI])**	9.7% (6.2% to 14.4%)	15.8% (13.3% to 18.4%)
Gestational age (wk), median (range)	39.0 (28.3 to 43.0)	39.0 (20.0 to 42.0)
Premature birth (% of infants [95% CI])††	15.0% (10.7% to 20.3%)	11.3% (9.2% to 13.5%)
Oral corticosteroid use		
Yes	32.7% (20.7% to 46.7%)	16.2% (10.9% to 21.4%)
No	9.6% (5.7% to 14.9%)	9.8% (7.5% to 12.1%)

*This EXPECT subcohort excludes pregnancies that terminated before 20 weeks' gestation and women with mild asthma severity, which are not available in the Quebec database.

†The QECC includes 2 twin pregnancies that each resulted in 1 live birth and 1 fetal death. Thus these 2 pregnancies are counted both in the number of pregnancies leading to live births and in the number of pregnancies leading to fetal death.

‡Defined as 20 weeks or greater gestation.

§Refer to Fig 1 for denominators of all infants, singletons, and twins.

||Only measurable for infants with nonmissing birth weight.

¶Low birth weight was defined as less than 2.5 kg.

#For the EXPECT study, defined by use of any oral corticosteroid as reported by the woman or prescriber. For the QECC, defined by 1 or more prescription fills for any oral corticosteroid.

**SGA was defined as a birth weight below the 10th percentile for the given gestational age at birth. For the EXPECT study, SGA is based on US standards,¹⁶ and for the QECC, SGA is based on Canadian standards.¹⁷

††Premature birth was defined as less than 37 weeks' gestation.

the QECC torticollis was reported within the musculoskeletal organ system. Other than torticollis, the most frequent major congenital anomalies in the EXPECT subcohort were congenital hydronephrosis (1.3% [n = 3]) and hypospadias (0.9% [n = 2]). Details on all major congenital anomalies, including those not in the subcohort, can be found in Table E1 in this article's Online Repository at www.jacionline.org.

Neonatal Platelet Count Substudy

Seventy-two infants were enrolled in the substudy; the median gestational age was 38.9 weeks (range, 31.7-41.6 weeks), and 16.7% were born prematurely. Among the 51 infants who had a sufficient blood sample to complete the substudy, the median age at platelet measurement was 23 days (range, 1-54 days), and 86% were sampled within 28 days of birth. Thrombocytopenia was not noted in any of the infants in the substudy; the median platelet count was 328×10^3 cells/ μ L (range, 150-609 $\times 10^3$ cells/ μ L), and all infants had platelet counts of greater than the lower limit of the reference ranges used by the central laboratory. The infant with an adverse event of thrombocytopenia (mentioned above) was not enrolled in the substudy.

DISCUSSION

Frequencies of live births and fetal deaths/stillbirths in the EXPECT subcohort were similar to those found in the QECC,

providing no evidence of increased risk of those outcomes associated with omalizumab use. The frequency of major congenital anomalies was 8.1% among singleton infants born to women with moderate-to-severe asthma in the EXPECT subcohort, which was similar to the frequency found in the QECC (8.9%).

Although the definitions of major anomalies were similar in the EXPECT study and the QECC, there were some meaningful differences. Classification was conservatively broad in the EXPECT study compared with the QECC, potentially leading to greater estimates in the EXPECT study than would have been reported under the QECC classification system. Specifically, among the 13 distinct types of major anomalies identified in the EXPECT study, 8 would be classified as major anomalies under the QECC, and the other 5 types (macrocephaly, concealed penis, hypospadias, pectus excavatum, and plagiocephaly) might have been classified in the QECC as either major or minor depending on severity. Nevertheless, the similar frequencies of major congenital anomalies in the EXPECT subcohort and in the QECC suggest that omalizumab use is not associated with an increase in the risk of major congenital anomalies in this population.

In the EXPECT study there was no evident pattern of major congenital anomalies that would have suggested a common underlying biologic pathway. The most commonly reported major congenital anomalies in the EXPECT study were torticollis (2.2%), hydronephrosis (1.3%), and hypospadias (0.9%).

TABLE V. Frequency of major congenital anomalies in singleton live-born infants by organ system (EXPECT subcohort and the QECC)

	EXPECT subcohort *† (n = 223), % (no. [95% CI])	QECC (n = 1124), % (no. [95% CI])
Infants with a major congenital anomaly	8.1% (18/223 [4.9% to 12.5%])	8.9% (102/1124 [7.0% to 10.8%])
All major congenital anomalies reported by organ system‡	No. (%)	No. (%)
Nervous system	1 (0.4%)	12 (1.1%)
Eye, ear, face, and neck§	5 (2.2%)	5 (0.4%)
Cardiac system	3 (1.3%)	32 (2.8%)
Circulatory system	1 (0.4%)	10 (0.9%)
Respiratory system	0	8 (0.7%)
Cleft lip and/or palate	0	3 (0.3%)
Digestive system	0	10 (0.9%)
Genital organs	3 (1.3%)	4 (0.4%)
Urinary system	4 (1.8%)	12 (1.1%)
Limbs	0	2 (0.2%)
Musculoskeletal§	2 (0.9%)	13 (1.2%)
Integument	1 (0.4%)	9 (0.8%)
Chromosomal	0	11 (1.0%)
Other	0	8 (0.7%)

*This EXPECT subcohort excludes pregnancies that terminated before 20 weeks' gestation and women with mild asthma severity, which are not available in the Quebec database.

†Among live infants not included in the table (twin infants and infants born to women with mild asthma, n = 17), there were 3 additional major congenital anomalies reported: 1 cardiac anomaly, 1 genital organ anomaly, and 1 urinary system anomaly.

‡Infants might have had more than 1 major congenital anomaly reported.

§Torticollis cases were classified as "face and neck" in the EXPECT study but as "musculoskeletal" in the QECC.

Previous studies found the prevalence of torticollis in infants to be approximately 8% to 16%, although the clinical definition of this condition varies, and identified cases likely include children with minor and easily correctable neck muscle imbalances.^{18,19} The prevalence of hypospadias among infants in North America has been reported as approximately 0.2% to 0.4% but with substantial variation by year and geographic region.^{20,21} Midtrimester ultrasonography detects fetal hydronephrosis in approximately 2% to 5.5% of infants.²² In a large population-based study conducted in Europe, hydronephrosis was recorded as a congenital anomaly for approximately 0.1% of newborn infants (reported as 9.8 per 100,000), although it was noted that diagnostic criteria vary substantially, leading to wide variability in reported frequency.^{22,23}

The frequency of premature birth was greater in the EXPECT subcohort than in the QECC (15.0% vs 11.3%). Nevertheless, the results for premature birth might reflect the underlying difference in prevalence of premature birth in the 2 countries. The rate of premature birth in the United States has ranged from 9.6% to 12.8% in analyses conducted between 2006 and 2016, whereas in Canada the rate was reported at 7.8% in 2013.²⁴⁻²⁶

The results might also be related to the prevalence of obesity in the EXPECT population, a known risk factor for premature delivery.²⁷ Indeed, obese women were more likely to have a premature birth (17.5%) than nonobese women (11%) in the EXPECT subcohort. Although data on obesity were not available in the QECC, the prevalence of obesity among pregnant women with asthma in the province of Quebec, the underlying population

for the QECC, has been reported to be substantially lower (between 12.2% and 16.2%) than that in the EXPECT subcohort (46.7% with a BMI ≥ 30 kg/m²).^{28,29} The prevalence in the EXPECT subcohort was also modestly higher than that found in another study of US pregnant women with asthma, which reported 42.4% of women with moderate-to-severe asthma having a BMI of 26 kg/m² or greater.³⁰

The prevalence of premature birth among women who did not take an oral corticosteroid was similar between the EXPECT subcohort and the QECC (9.6% and 9.8%, respectively), suggesting no association between omalizumab use and premature birth among women who did not take an oral corticosteroid. Among women who took any oral corticosteroid, the prevalence of premature birth was substantially greater in the EXPECT subcohort than in the QECC (32.7% and 16.2%, respectively). This difference likely contributed to the greater overall prevalence of premature birth in the EXPECT study (ie, 15.0% compared with 11.3% in the QECC). In previous studies women using oral corticosteroids or experiencing asthma exacerbations during pregnancy, which are both indicators of poorly controlled asthma, had a greater risk of premature birth (relative risk of 1.51 [95% CI, 1.15-1.98] for oral corticosteroids and 1.54 [95% CI, 0.89-2.69] for asthma exacerbations).³¹ Furthermore, women with inadequate asthma symptom control during the first part of pregnancy were significantly more likely to have a premature birth than women with adequate control (11.4% and 6.3%, respectively).³² The noted increased prevalence of premature birth among women in the EXPECT study who took any oral corticosteroid compared with those in the QECC (32.7% and 16.2%, respectively) might be a reflection of the oral corticosteroid treatment patterns (ie, dosage, frequency, and duration) for women in the EXPECT study, the majority of whom had severe asthma. However, neither data source provided the indication for the oral corticosteroid use, and EXPECT data were not sufficiently detailed to further characterize treatment patterns and cumulative exposure.

Infant outcomes related to birth weight varied between the EXPECT study and the QECC. In the EXPECT subcohort the proportion of infants born SGA was relatively low (9.7%) compared with the QECC (15.8%). The overall prevalence of low birth weight was greater in the EXPECT subcohort than in the QECC (13.7% vs 9.8%, respectively), yet the prevalence of low birth weight among full-term singletons in the EXPECT subcohort was similar to the prevalence in the QECC (2.7% and 2.9%, respectively). Given this lack of difference among full-term infants, it might be that the overall differences in low birth weight are related to the higher frequency of premature births in the EXPECT subcohort.

In the EXPECT Neonatal Platelet Count Substudy, thrombocytopenia was not noted in any of the infants. In the EXPECT registry subcohort (including infants not enrolled in the substudy), thrombocytopenia was reported in only 1 infant (0.4% [1/230]) compared with 0.6% (7/1124) reported in the QECC. These findings tend to confirm results in pooled analyses from 6 clinical trials of adolescents and adults that there was no evidence of a clinically relevant change in platelet counts after exposure to omalizumab.³³

Limitations of the study include those inherent to the design of pregnancy exposure registries. The EXPECT registry was voluntary and not population based, and thus it is difficult to know the extent to which findings can be extrapolated to other

populations of pregnant women with asthma exposed to omalizumab. In particular, other populations of pregnant women treated with omalizumab might have different frequencies of underlying risk factors for adverse pregnancy outcomes compared with women enrolled in the EXPECT study. The EXPECT registry attempted to reduce some biases that might be encountered in registries by prospectively enrolling women before the pregnancy outcome was known, ensuring timely collection of data soon after potential clinical events and ensuring a high retention rate through determination of pregnancy outcomes. Finally, this study was restricted to examining overall anomalies because the ability to identify risks for specific anomalies was limited given the number of pregnancies enrolled.

The EXPECT study, like many pregnancy exposure registries, did not include an internal control group, and therefore an external comparator, the QECC, was selected to provide a reference for the occurrence of outcomes in a similar population. This external comparator is important because the risk of some adverse pregnancy outcomes appears to be increased among pregnant women with moderate and severe asthma and among women who require systemic corticosteroids to manage their asthma.^{28,34-36} We attempted to minimize potential confounding bias that could explain differences (or lack of differences) between the EXPECT study and the QECC by restricting comparisons to women with moderate-to-severe asthma and age adjusting the results for the QECC. Women with severe asthma were more prevalent in the EXPECT study than in the QECC, which is consistent with use of omalizumab in patients whose symptoms were inadequately controlled with ICSs. As with any analysis that incorporates age standardization, residual confounding by age is still possible because risk can vary within each 5-year increment used for standardization. Because of the absence of some variables in the QECC and the EXPECT study, it was not possible to determine to what extent differences in study outcomes could be attributable to low socioeconomic status, obesity, and the frequency of tobacco and alcohol use, all of which can increase the risk of adverse pregnancy outcomes.³⁷ The definitions of congenital anomalies and asthma severity also differed between the EXPECT study and the QECC, and as noted earlier, the differences in definitions for congenital anomalies would have tended to provide a higher prevalence estimate in the EXPECT study relative to the QECC.

In conclusion, this comparative study found no evidence of a relationship between omalizumab exposure during pregnancy and increased risk of major congenital anomalies or thrombocytopenia in infants. The increased frequency of premature and low-birth-weight births in the EXPECT study might be attributable to population differences in the prevalence of underlying risk factors, such as obesity. Important limitations include the observational nature of the registry and potential differences between the registry population and the QECC. Despite the limitations, this comparison provides important and practical evidence-based information for clinicians and pregnant women with asthma who are considering omalizumab treatment.

Clinical implications: The similar frequencies of major congenital anomalies among infants whose mothers were exposed to omalizumab during pregnancy and those in a disease-matched comparator suggest that exposure during pregnancy is not associated with an increased risk.

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TABLE E1. Frequency of major congenital anomalies by organ system among live infants born to prospectively enrolled women with asthma in the EXPECT pregnancy registry

Organ system*	Specific anomaly	No. of infants (%) [n = 240]†
Circulatory	Arteriovenous malformation of skull/scalp	1 (0.4%)
Nervous system	Macrocephaly	1 (0.4%)
Eye, ear, face, and neck	Torticollis	5 (2.1%)
Cardiac system	Atrial septal defect	1 (0.4%)
	Patent foramen ovale‡	1 (0.4%)
	Ventricular septal defect	2 (0.8%)
Genital organs	Concealed penis	1 (0.4%)
	Hypospadias	3 (1.3%)
Musculoskeletal	Pectus excavatum	1 (0.4%)
	Plagiocephaly	1 (0.4%)
Urinary system	Hydronephrosis	3 (1.3%)
	Vesicoureteral reflux	2 (0.8%)
Integument	Cutaneous mastocytosis	1 (0.4%)

*No major anomalies were reported in the following organ systems: cleft lip and/or palate, conotruncal or obstructive heart, respiratory system, gastrointestinal system, female genitalia, limb reduction/addition defects, chromosome anomaly, other organs and organ systems, and specified syndromes/sequences/associations.

†Two infants had 2 major anomalies each, and 1 infant had 3 major anomalies.

‡Patent foramen ovale was considered a major anomaly if it persisted past 6 weeks of age and/or required medical or surgical intervention.