

The Xolair Pregnancy Registry (EXPECT): The safety of omalizumab use during pregnancy

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Background: For many asthma medications, pregnancy safety data remains insufficient.

Objective: The omalizumab pregnancy registry, EXPECT, evaluates maternal, pregnancy, and infant outcomes after exposure to omalizumab, including incidence of congenital anomalies.

Methods: EXPECT is a prospective, observational study of pregnant women exposed to ≥ 1 dose of omalizumab within 8 weeks prior to conception or at any time during pregnancy. Primary outcome measures include rates of live births, elective terminations, stillbirths, and congenital anomalies. Data were collected at enrollment, each trimester, birth, and every 6 months up to 18 months post-delivery.

Results: As of November 2012, 188 of 191 pregnant women were exposed to omalizumab during their first trimester. Of 169 pregnancies with known outcomes (median exposure during pregnancy, 8.8 months), there were 156 live births of 160 infants (4 twin pairs), 1 fetal death/stillbirth, 11 spontaneous abortions, and 1 elective termination. Among 152 singleton infants, 22 (14.5%) were born prematurely. Of 147 singleton infants with weight data, 16 (10.9%) were small for gestational age. Among 125 singleton full-term infants, 4 (3.2%) had low birth weights. Overall, 20 infants had congenital anomalies confirmed, 7 (4.4%) of whom had 1 major defect. No pattern of anomalies was observed.

Conclusions: To date, proportions of major congenital anomalies, prematurity, low birth weight, and small size for gestational age observed in the EXPECT registry are not inconsistent with findings from other studies in this asthma population. Recognizing the small sample size available, no

apparent increased birth prevalence of major anomalies or patterns of major anomalies has been observed. (*J Allergy Clin Immunol* 2014;■■■:■■■-■■■.)

Key words: Omalizumab, pregnancy, moderate-to-severe persistent allergic asthma

Asthma affected 8.4% to 8.8% of pregnant women in the United States between 2000 and 2003.¹ Uncontrolled asthma during pregnancy can increase the risk of perinatal mortality, congenital anomalies, prematurity, low birth weight, and adverse maternal outcomes.²⁻⁴ Evidence of teratogenic risk for most asthma medications is limited.⁵⁻⁷ Studies have shown that the use of theophylline, inhaled or oral corticosteroids, β_2 -agonists, or montelukast is not associated with an increased risk of fetal abnormalities when monitored appropriately.^{5,7} A systematic literature review reported that although negative pregnancy outcomes associated with asthma medication use have been reported, it remains unclear whether a direct causal link exists due to potential confounding by the underlying disease.⁸ It is generally considered safer for pregnant asthmatic women to be treated than to have asthma symptoms and exacerbations.⁴ Therefore, decisions to treat asthma during pregnancy should evaluate the risks and benefits of medication.

Omalizumab, a recombinant monoclonal anti-IgE antibody, is licensed in the United States as an add-on therapy for the treatment of patients (aged ≥ 12 years) with moderate-to-severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids (ICS).⁹ In the European Union, omalizumab is approved for patients ≥ 6 years of age with severe persistent allergic asthma inadequately controlled with ICS and long-acting β_2 -agonists (LABA).¹⁰ Omalizumab is classified as a Pregnancy Category B medication in US prescribing instructions; the safety of omalizumab exposure during pregnancy in humans has not been evaluated. In preclinical reproduction studies in cynomolgus monkeys, omalizumab was not associated with maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis. Furthermore, omalizumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing.

EXPECT, an omalizumab pregnancy registry, is a post-marketing commitment to the US Food and Drug Administration (FDA) designed to evaluate health outcomes, including the incidence of congenital anomalies, in pregnant women and their infants.

METHODS

Study design

The primary objective of EXPECT is to evaluate pregnancy outcomes, including elective terminations, stillbirths (≥ 20 weeks' gestation), and

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Abbreviations used

HCP:	Health care provider
ICS:	Inhaled corticosteroids
LABA:	Long-acting β_2 -agonist
MACDP:	Metropolitan Atlanta Congenital Defects Program
SGA:	Small for gestational age
US:	United States
FDA:	US Food and Drug Administration

congenital anomalies (major or conditional). Secondary objectives are to estimate the risk of spontaneous fetal loss, the occurrence of other pregnancy or delivery complications or abnormalities, and neonate/infant outcomes, and to explore the potential risk to newborn infants exposed to omalizumab prenatally or both prenatally and via breast milk.

EXPECT is an observational, single-cohort study of pregnant women exposed to ≥ 1 dose of omalizumab within 8 weeks prior to conception (due to omalizumab's half-life of 26 days⁹) or at any time during pregnancy. In accordance with the FDA's Guidance for Industry on Establishing Pregnancy Exposure Registries, women have been prospectively enrolled if they contacted the registry before receiving any prenatal testing results that may have increased the likelihood of pregnancy monitoring. Prior knowledge of prenatal testing results can introduce a source of bias. Thus, women with knowledge of an abnormal prenatal test result at the time of registry contact are considered to be retrospective cases in the registry. Their data are taken into account for detection of any patterns of events suggestive of a common etiology but excluded from the primary analysis.

Enrollment is voluntary and initiated by the pregnant woman; informed consent to participate is obtained from all women. Approval of EXPECT by the Western Institutional Review Board (Olympia, Wash) is reviewed annually. Women who were not pregnant at the time of first contact (ie, enrollment) were not eligible for the registry. Any miscarriage, spontaneous abortion, or elective termination that occurred after enrollment was recorded in the database. Information is collected via telephone from women and their health care providers (HCP). Registry data are reviewed semi-annually by an external advisory committee, including specialists in teratology, pharmacoepidemiology, pediatrics, asthma/allergy, neonatology, and obstetrics/gynecology. The committee may make recommendations on registry conduct.

EXPECT will continue until at least 250 pregnant women have been prospectively enrolled. A variety of recruitment strategies are being used to inform pregnant women and their HCPs about the EXPECT registry. Patients participating in active omalizumab trials are notified about the study. In addition, registry details can be found in the product's package insert and at related Internet sites; announcements in professional magazines, journals, and newsletters; exhibits at professional meetings; and personal correspondence with specialists. Based on the current recruitment rate, the registry is not projected to complete enrollment until 2017, and longitudinal data collection will not be complete until 2018 or beyond.

Inclusion criteria. A registrant must have a current pregnancy with omalizumab exposure within 8 weeks prior to conception or at any time during the pregnancy, be willing to provide informed consent for participation, and agree that the registry may contact her HCPs.

Assessments

Relevant data about each woman's medical history, pregnancy, and asthma are collected from her and her HCPs at the time of enrollment, at each pregnancy trimester, and at delivery or on termination of the pregnancy. After delivery, equivalent data are collected for infants at birth, 6 months, and 12 months post-delivery (and up to 18 months if the woman is breastfeeding). Data gathered include information on pregnancy status, prenatal testing, omalizumab exposure, other medication use, pregnancy outcome, and any complications, delivery method, neonatal gender, infant anthropometry, and congenital anomalies.

All reports of potential congenital anomalies are reviewed by an independent, external teratology expert on an ongoing basis during the course of the study, using a categorization system based on Metropolitan Atlanta Congenital Defects Program (MACDP) definitions.¹¹ Defects are classified as major or as conditional. Major defects are defined as anomalies that have either cosmetic or functional significance to the child. Conditional defects are defined as common deviations from normal structure or function that are unlikely to require medical or surgical intervention. The MACDP collects cases only with major malformations, regardless of the presence of conditional anomalies. This registry follows these guidelines but additionally considers infants with ≥ 2 conditional anomalies to meet the MACDP criteria.

In addition, all serious adverse events and targeted adverse events were monitored. An adverse event was defined as serious if it resulted in death or was life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability, resulted in a congenital anomaly in an infant born to a woman exposed to omalizumab, or was considered a significant medical event by the principal investigator. The only targeted adverse events were signs or symptoms suggestive of thrombocytopenia in the neonate. In non-human primates, supra-pharmacologic doses of omalizumab have been shown to decrease blood platelet levels, particularly in younger animals. Thus, a developing human fetus and neonate may represent more sensitive target populations.

Statistical analysis

The EXPECT registry is an observational cohort study intended for signal detection. The scope and design of the study were developed based on the FDA post-marketing commitment. Because there is no internal comparator group, the data for selected outcome measures are summarized using descriptive statistics with 95% CI to convey the level of certainty associated with these estimates. The primary analysis for all pregnancy outcomes includes only prospectively enrolled eligible women and excludes outcomes in subsequent pregnancies for women who re-enroll in the registry. Owing to selection bias and recall bias introduced by retrospectively reported data, women enrolled retrospectively are excluded from the primary analysis.

The studies listed in Table I were selected to be representative of birth and pregnancy outcomes in the general population—including national statistical surveys data and US-based and international birth anomaly registries—and populations with asthma, which included reports from the main US-based source of pregnancy and birth outcomes, the Organization of Teratology Information Specialists.

RESULTS

Cumulative registry data for 191 women who were prospectively enrolled from September 29, 2006 through November 30, 2012 are included in this report. Demographics and clinical characteristics of the enrolled patients are shown in Table II. Of the 191 evaluable pregnancies, 61.8% were enrolled during the first trimester, 31.4% during the second trimester, and 6.8% during the third trimester. The average gestational age at enrollment was 13.8 weeks. At the time of data cut-off, data on pregnancy outcomes were available for 169 women, 12 were continuing follow-up, and 10 had discontinued participation in the registry before pregnancy outcomes were known.

Exposure to omalizumab

Of 191 pregnant women, 188 were exposed to omalizumab during their first trimester of pregnancy, and 3 had their earliest exposure in the second trimester. The dosing interval was evenly distributed between every 2 weeks (48.0%) and every 4 weeks (48.6%). The median duration of omalizumab exposure during pregnancy was 8.8 months (range, 1.1 to 9.9 months) for the 169 pregnancies with a known outcome. Ninety-eight infants were

TABLE I. EXPECT findings compared with those from studies of adverse pregnancy outcomes in the general population and in women with asthma

Data source	Citation	Major congenital anomalies	Preterm birth	Small for gestational age	Low birth weight	Fetal death	Spontaneous abortion
			(<37 wks) (per 100 births)	(per 100 births)	(<2500 g)	(>20 wks) (per 100 pregnancies)	(<20 wks)
EXPECT		4.4 (1.8-8.8)	14.5 (9.3-21.1)	10.9 (6.4-17.1)	3.2 (0.9-8.0)	0.60 (0-3.3)	8.6 (4.4-14.9)
General population							
MACDP	Correa 2007 ³² ; Rynn 2008 ²⁵	2.8 ³²	7.1 ²⁵		7.7 ²⁵		
CBDMP	Calif Dept Public Health ³³	2.9					
NYSCMR	NY Dept Public Health ³⁴	3.1					
TBDR	Tex Dept State Health ³⁵	4.2					
DNBR/DNPR	Pasternak 2013 ¹⁸	2.9	5.2	9.2	3.7	0.40	
NCHS	Martin 2013 ²⁴ ; MMWR ²³ ; MacDorman 2012 ¹⁹		11.7 ²⁴	10.5 ²³	8.1 ²⁴	0.61 ¹⁹	
Kaiser Permanente	Ammon Avalos 2012 ²⁸						11-22
Asthma population							
ISQ	Blais 2009 ¹⁶ ; Blais 2007 ¹⁷						
MED-ECHO	All asthma	6.1 ¹⁶					
RAMQ	ICS (≤1000 µg)	5.7 ¹⁶					
	ICS (>1000 µg)	8.3 ¹⁶					
	OCS	7.3 ¹⁷					
	SABA	6.1 ¹⁷					
	LABA	9.1 ¹⁷					
OTIS Network	Bakhireva 2007 ¹⁵						
	β ₂ -agonists	3.9	11.8	3.9		0	5.6
	LTRAs	6.0	9.8	6.1		1.1	5.6
Soroka Univ Med Ctr	Sheiner 2005 ²⁷	3.8			9.5		
Int'l Teratogen Information Services	Sarkar 2009 ²⁶	2.7			18.2		9.4
Health Improvement Network Database (UK)	Tata 2007 ²⁰					1.1	

CBDMP, California Birth Defects Monitoring Program; Dept, Department; DNBR, Danish National Birth Registry; DNPR, Danish National Patient Registry; ISQ, Institut de la Statistique du Québec; LTRA, leukotriene receptor antagonists; MED-ECHO, Maintenance et Exploitation des Données pour l'étude de la clientèle hospitalière; NCHS, National Center for Health Statistics; NYSCMR, New York State Congenital Malformations Registry; OCS, oral corticosteroids; OTIS, Organization of Teratology Information Specialists; RAMQ, Régie de l'assurance-maladie du Québec; TBDR, Texas Birth Defects Registry; UK, United Kingdom.

exposed to omalizumab through breastfeeding, with a median omalizumab exposure duration of 3.9 months. Details regarding omalizumab exposure for enrolled women and infants are shown in Table III.

Pregnancy outcomes

Pregnancy outcomes are shown in Table IV. Of 169 pregnancies with a known outcome, there were 156 live births, with a total of 160 infants (including 4 twin pairs), 1 fetal death/stillbirth (0.6%; 95% CI: 0, 3.3%), 11 spontaneous abortions (8.6%; 95% CI: 4.4, 14.9%), and 1 elective termination. The risk of spontaneous abortions was conservatively estimated by excluding those who enrolled after 20 weeks of fetal gestation.

Live birth outcomes

Live birth outcomes are shown in Table V. The mean gestational age for all 160 infants was 38.3 weeks. The rates of infants with prematurity, low birth weight, and small size for gestational age (SGA) are reported for singletons. Among 152 singleton infants, 22 (14.5%; 95% CI: 9.3, 21.1%) were born prematurely (<37 weeks). Among 147 singleton infants with birth weight data available, 16 (10.9%) were SGA. Among 125 full-term singleton infants, 4 (3.2%) had low birth weights.

Birth weight was also summarized by including both singletons and twins with birth weight data available. For 127 full-term

infants, the mean ($\pm$ SD) birth weight was 3.3 ± 0.5 kg; 6 (4.7%) had a low birth weight (defined as <2.5 kg). For 28 premature infants, the mean ($\pm$ SD) birth weight was 2.3 ± 0.6 kg; 19 (67.9%) had a low birth weight.

Among the 160 live births in prospectively enrolled women, 21 anomalies were confirmed in 20 infants by an external teratologist. Seven anomalies in 7 infants were determined to be major congenital defects (Table VI). Eighteen additional anomalies occurring in 14 infants were determined to be conditional birth defects (Table VI). Ankyloglossia was the most common conditional birth defect reported ($n = 6$). Three infants had multiple conditional defects: benign pigmented nevus plus pilonidal dimple; undescended testes plus hypoplasia of the scrotum; preauricular skin tags plus umbilical hernia plus hydrocele. Nine other potential anomalies in 7 different infants were determined not to be defects. Among infants born to retrospectively enrolled women ($n = 10$), there were 2 confirmed major defects. One infant born at 39.0 weeks' gestation had multicystic dysplastic kidney; another infant born at 39.4 weeks' gestation had torticollis.

Other safety outcomes

There were no maternal deaths. Neonatal thrombocytopenia was reported in 1 infant (0.6%) born at 37.7 weeks to a woman who experienced preeclampsia and respiratory failure

TABLE II. Registrant demographics and clinical characteristics at enrollment

	All patients (N = 191)
Mean (SD) age (y)	30.1 (5.8)
Age (y), n (%)	
<18	5 (2.6)
18-34	139 (72.8)
35-44	46 (24.1)
>44	1 (0.5)
Race, n (%) ^a	
White	146 (77.2)
Black or African American	22 (11.6)
Other	21 (11.1)
Pre-pregnancy mean (SD) body weight, kg ^b	79.2 (22.0)
Pre-pregnancy BMI ≥ 30 , n (%) ^c	48 (47.1)
Smoking within 1 mo of conception up to enrollment, n (%)	11 (5.8)
Currently drinking (%) [*]	
No. of patients	189 (99.0)
1 drink per day	1 (0.5)
Not collected	1 (0.5)
Previous pregnancy history, n (%) ^d	
Full-term birth	85 (76.6)
Elective termination	14 (12.6)
Spontaneous abortion	45 (40.5)
Stillborn/fetal death	1 (0.9)
Premature birth	12 (10.8)
Birth defects	7 (6.3)
Physician-assessed severity of asthma, n (%) ^e	
Mild	4 (2.7)
Moderate	47 (31.3)
Severe	99 (66.0)

^an = 189.^bn = 121.^cn = 102.^dn = 111.^en = 150.

BMI, Body mass index.

^{*}Assessed at enrollment.

necessitating a Caesarean section. The newborn's platelet count at the time of the event was not reported, but it was documented to be in the normal range 1 month later. Collection of other serious adverse events is ongoing and will be reported when the study is completed.

DISCUSSION

Asthma is a common chronic condition that frequently occurs during pregnancy. Current guidelines recommend that the goal of treatment for all women, pregnant or not, is to provide optimal therapy to maintain disease control while ensuring the safety of the mother and fetus.⁴ In the National Heart, Lung, and Blood Institute's guidelines for the pharmacologic management of asthma in pregnant women, the National Asthma Education and Prevention Program's Asthma and Pregnancy Working Group performed a systematic review of the literature and concluded that it is safer to treat asthma in pregnant women than for them to experience asthma symptoms and exacerbations. Indeed, some evidence suggests that uncontrolled asthma itself is associated with adverse perinatal outcomes, including impaired fetal growth.¹²⁻¹⁴ Still,

TABLE III. Omalizumab exposure in registrants

	All registrants (N = 191)
Dose (mg), ^a n (%)	
150	37 (21.5)
225	23 (13.4)
300	56 (32.6)
375	31 (18.0)
Other	25 (14.5)
Dosing interval, ^b n (%)	
Every 2 weeks	83 (48.0)
Every 4 weeks	84 (48.6)
Other	6 (3.5)
Earliest exposure, n (%)	
First trimester	188 (98.4)
Second trimester	3 (1.6)
Third trimester	0 (0.0)
Timing of exposure, ^c n (%)	
First trimester	21 (12.7)
Second trimester	0 (0.0)
Third trimester	0 (0.0)
First and second trimesters	4 (2.4)
First and third trimesters	2 (1.2)
Second and third trimesters	3 (1.8)
All trimesters	135 (81.8)
Exposure duration (mo) during pregnancy ^d	
Mean (SD)	7.3 (2.7)
Median (range)	8.8 (1.1-9.9)
Infant exposure via breastfeeding, n (%) ^e	
Delivery through mo 6	98 (100)
Month 6 through mo 12	43 (43.9)
Beyond mo 12	16 (16.3)
Exposure duration (mo) in breastfed infants ^e	
Mean (SD)	5.4 (5.1)
Median, range	3.9 (0.1-20.4)

^an = 172.^bn = 173.^cn = 165.^dn = 169 pregnancies with an outcome.^en = 98 infants with omalizumab exposure through breastfeeding.^{*}Assessed at enrollment.**TABLE IV.** Known pregnancy outcomes for registrants^{*}

Outcome	Pregnancies (N = 169)
Live birth, n	156 [†]
Percentage of registrants (95% CI)	92.3 (87.2, 95.8)
Elective termination, n	1
Percentage of registrants (95% CI)	0.6 (0.0, 3.3)
Stillborn/fetal death (≥ 20 wk), n	1
Percentage of registrants (95% CI)	0.6 (0.0, 3.3)
Spontaneous abortion (<20 wk)	11
Registrants enrolled prior to 20 wks, n	128
Percentage of registrants (95% CI)	8.6 (4.4, 14.9)

^{*}One pregnancy per woman.[†]One hundred fifty-two singleton infants and 4 pairs of twins.

data regarding the safety of many asthma medications during pregnancy is limited.

The objective of the EXPECT study is to collect human safety data on omalizumab use during pregnancy. Primarily, the registry monitors the occurrence of congenital anomalies, elective terminations, and fetal deaths. Secondary pregnancy outcomes include preterm birth, SGA, low birth weight, and spontaneous

TABLE V. Neonatal outcomes

Outcome	N	% (95% CI)
All infants	160	
Singleton infants	152	
Premature birth (<37 wk)	22	14.5 (9.3, 21.1)
Small for gestational age*	16†	10.9 (6.4, 17.1)
Low birth weight (<2.5 kg)	4‡	3.2 (0.9, 8.0)
Infants with major or conditional defects§		
Major birth defects	7	4.4 (1.8, 8.8)
Conditional defects¶	14	8.8 (4.9, 14.2)

*Birth weight below the 10th percentile for the given gestational age at birth.³¹

†n = 147 singleton infants with birth weight data available.

‡n = 125 singleton infants with birth weight data available.

§One infant had both a major defect and a conditional defect.

||Major defects are defined as potential anomalies determined to be major defects that have either cosmetic or functional significance to the child after review by an external teratologist.

¶Conditional defects are defined as common deviations from normal function or structure that are unlikely to require intervention of a surgical or other medical nature or are frequently encountered in premature infants; they primarily (but not exclusively) comprise minor defects.

abortions. EXPECT data collected to date are summarized in Table I, which also includes data from other birth registries and the published literature. For major congenital anomalies, the observed prevalence in EXPECT (4.4%) is not inconsistent with rates reported for general populations (range, 2.8% to 4.2%) or populations with asthma (range, 2.7% to 9.1%). Further, within populations with asthma, rates of major defects were similar, regardless of treatment.¹⁵⁻¹⁷ Two studies showed a trend toward higher defect rates among persons with asthma taking ICS doses >1000 µg (8.3%)¹⁶ and LABAs (9.1%).¹⁷

For fetal deaths, the observed prevalence in EXPECT (0.60%) was similar to the general population in a Danish registry (0.40%)¹⁸ and North American statistics from the Centers for Disease Control and Prevention (0.61%).¹⁹ Prevalence estimates of fetal death rates in populations with asthma were slightly higher (1.1%).^{15,20}

For secondary outcomes, the preterm birth rate for singleton infants in EXPECT was 14.5% (Table I). A recent meta-analysis of studies published between 1975 and 2009 showed a 40% increase in risk for preterm delivery among pregnant woman with asthma compared with those without asthma (relative risk [RR], 1.41 [95% CI: 1.23-1.62]).²¹ Further, pregnant women with asthma using oral corticosteroids or experiencing asthma exacerbations during pregnancy (both indicators of poorly controlled asthma) had an even higher risk of preterm delivery, with a RR of 1.51 (95% CI: 1.15-1.98) for oral corticosteroids and 1.54 (95% CI: 0.89-2.69) for asthma exacerbations.²² The mean gestational age for live births among prospectively enrolled participants was 38.3 weeks. Previous studies have reported mean gestational ages ranging from 37.4 to 39.4 weeks for women with asthma.²²⁻²⁴

The SGA rate in EXPECT was 10.9%, which is consistent with rates reported for the general population^{18,23} and higher than the rate reported for another asthma registry, which was below the general population rates¹⁵ (Table I). Among registrants who had full-term deliveries, the proportion with low birth weight infants was 3.2%, which compares most closely with the rate from the Danish registry.¹⁸ Reported rates from other populations, both general and with asthma, varied widely²⁴⁻²⁷ (Table I). In a recent

TABLE VI. Major and congenital defects observed

Teratologist assessment	Description
Major defect	Hypospadias (n = 2) Arteriovenous malformation Bilateral renal pelvis dilation Cutaneous mastocytosis Patent foramen ovale* Vesicoureteral reflux
Conditional defect	Ankyloglossia (n = 6) Umbilical hernia (n = 2) Benign pigmented nevus Bilateral inguinal hernia Hypoplasia of scrotum Hydrocele Immature eye duct Pilonidal dimple Positional plagiocephaly Preauricular skin tags Stahl ear Undescended testes

*Considered a major defect because it persisted past 6 weeks of age in a full-term infant.

meta-analysis in which pregnant women were classified by asthma severity or number of medications used to control asthma symptoms, women with moderate-to-severe asthma were at increased risk of SGA (RR, 1.24 [95% CI: 1.15-1.35]) and low birth weight (RR, 1.15 [95% CI: 1.05-1.25]).²² Despite enrolling predominantly moderate-to-severe asthmatic patients, the rates of SGA and low birth weight observed in EXPECT do not appear elevated much beyond that expected for the general population. The rate of spontaneous abortions in EXPECT (8.6%) was within the range reported for the general populations (11% to 22%)²⁸ and populations with asthma (5.6%, 9.4%).^{15,26}

One possible explanation for the increased risk for poor perinatal outcomes is that uncontrolled asthma during pregnancy may lead to fetal hypoxia.²¹ Data from 2 large, population-based studies suggested that asthma severity and potential episodes of hypoxia may have accounted for an increased risk in specific congenital abnormalities.^{2,29} In EXPECT, most of the women were classified as having moderate-to-severe asthma; however, based on the information collected, it was not possible to determine whether fetal hypoxia played a role in the specific defects observed.

Strengths of this study include the prospective identification of exposed pregnancies, ascertainment of key clinical information and outcomes from both the participating woman and her HCP, and a relatively low rate of loss to follow-up before the pregnancy outcome. Moreover, information on every potential abnormal infant outcome was carefully reviewed by an independent teratologist, including appropriate follow-up to gather additional clinical details and classification of abnormal outcomes using a well-recognized classification scheme.¹¹

Limitations of this study include those inherent to the design of a voluntary registry; also, the number of asthmatic women who become pregnant while taking omalizumab is not large. Thus, participation is strictly determined by women and/or their HCPs who learn about the registry and are inclined to enroll. Complete information for certain outcomes was not available for all participants despite multiple follow-up attempts, and the extent to which missing data may be related to any given outcome might be a potential source of bias.

This study is also limited by the lack of an internal comparison group. Although external comparators were used to provide context for our study results, most of the cohorts identified for comparison did not include women with similar asthma severity; thus, it was a challenge to determine whether the pregnancy outcomes observed were the result of having more severe asthma that requires treatment with omalizumab. Differences in estimates may also be due to differences in study methods, data collection, or outcome ascertainment.

Studies that seek to evaluate medication exposure and birth defects are confronted with the problem of sample size. The effect of human teratogens is usually specific to individual or small groups of birth defects. Specific birth defects are rare; many have expected frequencies of 1/1000 live births or fewer.³⁰ An increase in the frequency of a specific medication-related defect is unlikely to be reflected in an increase in the frequency of total birth defects, which occur in 3% to 5% of all births. Therefore, although the prevalence of total birth defects in the cases prospectively reported in EXPECT did not differ from the expected prevalence, and there was no pattern of birth defects observed, the study cannot rule out increases in the risk of individual birth defects.

Based on data collected to date, the prevalence of major congenital defects in EXPECT continues to be no higher than those reported in the general population with asthma. In addition, omalizumab does not appear to increase the risk of preterm birth or SGA infants beyond that seen in the general asthma population. Additional results will be reported as the study continues to accrue patients and outcome information.

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Clinical implications: EXPECT results are not inconsistent with pregnancy outcomes complicated by asthma. The safety profile of omalizumab treatment during pregnancy must be weighed against the risks of uncontrolled asthma.

REFERENCES

1. Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. *Immunol Allergy Clin North Am* 2006;26:29-62.
2. Blais L, Kettani FZ, Elftouh N, Forget A. Effect of maternal asthma on the risk of specific congenital malformations: A population-based cohort study. *Birth Defects Res A Clin Mol Teratol* 2010;88:216-22.
3. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 1998;158:1091-5.
4. National Heart Lung and Blood Institute. NAEP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. *J Allergy Clin Immunol* 2005;115:34-46.
5. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. *Hum Exp Toxicol* 2006;25:447-52.
6. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 1997;100:301-6.
7. Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, et al. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. *Thorax* 2008;63:981-7.
8. Lim A, Stewart K, König K, George J. Systematic review of the safety of regular preventive asthma medications during pregnancy. *Ann Pharmacother* 2011;45:931-45.
9. Genentech Inc. XOLAIR [omalizumab]: Full Prescribing Information. 2010.
10. European Medicines Agency. Xolair: European Public Assessment Report (EPAR). 2013.
11. Scheuerle A, Tilson H. Birth defect classification by organ system: a novel approach to heighten teratogenic signalling in a pregnancy registry. *Pharmacoepidemiol Drug Saf* 2002;11:465-75.
12. Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol* 2005;106:1046-54.
13. Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. Kaiser-Permanente Asthma and Pregnancy Study Group. *Chest* 1990;98:389-92.
14. Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. *Am J Respir Crit Care Med* 1995;151:1170-4.
15. Bakhireva LN, Jones KL, Schatz M, Klonoff-Cohen HS, Johnson D, Slymen DJ, et al. Safety of leukotriene receptor antagonists in pregnancy. *J Allergy Clin Immunol* 2007;119:618-25.
16. Blais L, Beauchesne MF, Lemiere C, Elftouh N. High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations. *J Allergy Clin Immunol* 2009;124:1229-34.e4.
17. Blais L, Beauchesne MF, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. *Thorax* 2007;62:320-8.
18. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med* 2013;368:814-23.
19. MacDorman M, Kirmeyer S, Wilson E. Fetal and perinatal mortality, United States, 2006. Bethesda, Md: Centers for Disease Control and Prevention; 2012; 1-23.
20. Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, et al. A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *Am J Respir Crit Care Med* 2007;175:991-7.
21. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011;118:1314-23.
22. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J* 2013;41:1082-90.
23. QuickStats: Percentage of small-for-gestational-age births, by race and Hispanic ethnicity—United States, 2005. *MMWR Morb Mortal Wkly Rep* 2008;57:1359.
24. Martin J, Hamilton B, Ventura S, Osterman M, Mathews T. Births: Final Data for 2011. Bethesda, MD: Centers for Disease Control and Prevention; 2013:1-70.
25. Rynn L, Cragan J, Correa A. Update on overall prevalence of major birth defects—Atlanta, Georgia, 1978-2005. *MMWR Morb Mortal Wkly Rep* 2008; 57:1-5.
26. Sarkar M, Koren G, Kalra S, Ying A, Smorlesi C, De Santis M, et al. Montelukast use during pregnancy: a multicentre, prospective, comparative study of infant outcomes. *Eur J Clin Pharmacol* 2009;65:1259-64.
27. Sheiner E, Mazor M, Levy A, Wiznitzer A, Bashiri A. Pregnancy outcome of asthmatic patients: a population-based study. *J Matern Fetal Neonatal Med* 2005;18:237-40.
28. Ammon Avalos L, Galindo C, Li DK. A systematic review to calculate background miscarriage rates using life table analysis. *Birth Defects Res A Clin Mol Teratol* 2012;94:417-23.
29. Lin S, Munsie JP, Herdt-Losavio ML, Druschel CM, Campbell K, Browne ML, et al. Maternal asthma medication use and the risk of selected birth defects. *Pediatrics* 2012;129:e317-24.
30. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol* 2010;88:1008-16.
31. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol* 1996;87:163-8.
32. Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, et al. Reporting birth defects surveillance data 1968-2003. *Birth Defects Res A Clin Mol Teratol* 2007;79:65-186.
33. California Birth Defects Monitoring Program. Birth Defects in California: 1983-1990. Sacramento: California Department of Public Health; 1994.
34. Congenital Malformation Registry. Statistical Summary of Children Born in 1983-2007. Albany: New York State Department of Health; 2013.
35. Texas Birth Defects Registry. Report of Birth Defects Among 2000-2009 Deliveries, Table 1. Prevalence of Selected Birth Defects, Texas, 2000-2009. Austin, Tex: Texas Department of State Health; 2012.