

Letter to the Editor

Congenital malformations among infants born to women receiving montelukast, inhaled corticosteroids, and other asthma medications

To the Editor:

Asthma is one of the most common health conditions that might complicate pregnancy, and poorly controlled asthma poses substantial risks to both maternal and fetal health,¹ including increased risk of congenital anomalies.² Because inadequate asthma control poses a greater risk to fetal health than do asthma medications, current asthma and obstetric guidelines recommend using effective drug therapy to control asthma.^{1,3}

Data suggest that commonly used asthma medications, such as inhaled corticosteroids (ICSs), short-acting β -agonists,⁴ and montelukast,^{5,6} are not associated with adverse perinatal outcomes. Through worldwide postmarketing surveillance conducted by Merck (from initial approval in July 1997 through June 2006), 6 reports were identified of limb-reduction defects in

live-born offspring of women receiving montelukast during pregnancy.⁷ Independent reviews by 3 experts in congenital malformations, including 2 specialists in human limb defects, concluded these shared a similar presentation broadly termed “limb reduction” or “transverse terminal limb defects.” They noted there were no compelling data to indicate a known biological mechanism by which montelukast could have increased the risk of these defects. For instance, montelukast preclinical studies in rats and rabbits at doses approximately 100 times the maximum recommended oral doses in adults demonstrated no teratogenicity, including limb defects.⁸ No additional reports of limb defects have been received since June 2006. Although these data do not support a causal association between montelukast use and major teratogenic effects, no alternative explanations (eg, risk factors for limb-reduction defects⁹ or other anomalies associated with limb defects¹⁰) accounted for these 6 limb defects.

To better quantify the prevalence of congenital anomalies in infants born to mothers exposed to montelukast during pregnancy,

TABLE I. Demographic characteristics and prenatal attributes

	Montelukast		ICSs		Other asthma medications		Asthma diagnosis only		Reference	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Deliveries	1,504		3,802		8,583		2,038		37,769	
Infants	1,535		3,918		8,834		2,092		38,828	
Age (y)										
<20	14	0.9	28	0.7	108	1.3	39	1.9	425	1.1
20-29	492	32.7	1,151	30.3	3,281	38.2	829	40.7	14,231	37.7
30-39	902	59.9	2,376	62.5	4,773	55.6	1,075	52.8	21,459	56.8
≥40	96	6.5	247	6.5	421	4.9	95	4.7	1,654	4.4
Asthma medications*										
SABA	819	54.5	2,471	65.0	7,693	92.8	NA	NA	NA	NA
LABA	162	10.8	435	11.4	236	2.7	NA	NA	NA	NA
LABA + ICS	295	19.6	1,061	27.9	0	0.0	NA	NA	NA	NA
ICS	379	25.2	2,640	69.4	0	0.0	NA	NA	NA	NA
OCS	302	20.1	779	20.5	928	10.8	187	9.2	NA	NA
IV steroids	86	5.7	129	3.4	241	2.8	74	3.6	NA	NA
Mast cell stabilizers	47	3.1	72	1.9	134	1.6	NA	NA	NA	NA
Xanthines	40	2.7	81	2.1	59	0.7	NA	NA	NA	NA
Zafirlukast	8	0.5	40	1.1	43	0.5	NA	NA	NA	NA
Prenatal attributes										
Multiple gestation	34	2.3	101	2.7	220	2.6	50	2.5	1,008	2.7
Asthma physician visits	622	41.4	1,689	44.4	1,538	17.9	1,149	56.4	NA	NA
Asthma hospitalization	41	2.7	135	3.6	107	1.2	39	1.9	NA	NA
Amniocentesis	152	10.1	474	12.5	846	9.9	211	10.4	3,402	9.0
CVS	15	1.0	36	0.9	60	0.7	13	0.6	249	0.7
High-risk pregnancy	403	26.8	958	25.2	2,095	24.4	556	27.3	7,974	21.1
Early or threatened labor	456	30.3	1,147	30.2	2,829	33.0	734	36.0	9,908	26.2
Hemorrhage in early pregnancy	326	21.7	832	21.9	1,821	21.2	477	23.4	7,086	18.8
Antepartum hemorrhage, abruptio placenta, placenta previa	178	11.8	464	12.2	1,045	12.2	272	13.3	4,064	10.8
Excessive vomiting in pregnancy	92	6.1	206	5.4	495	5.8	200	9.8	1,746	4.6
Diabetes	149	9.9	297	7.8	670	7.8	182	8.7	2,298	6.1
Hypertension	166	11.0	351	9.2	837	9.8	223	10.9	2,258	6.0
Mental disorders	310	20.6	643	16.9	1,434	16.7	310	14.9	3,601	9.5
Teratogenic drug	130	8.6	289	7.6	559	6.5	119	5.7	1,465	3.9
Smoking	7	0.5	28	0.9	48	1.8	27	1.3	117	0.3
Alcohol use	0	0.0	9	0.3	6	0.1	3	0.1	25	0.1

CVS, Chorionic villus sampling; IV, intravenous; LABA, long-acting β -agonist; OCS, oral corticosteroid; SABA, short-acting β -agonist.

*Medications with 1.0% or greater use in a group. Does not include dispensings before the first day of the estimated pregnancy interval.

TABLE II. Number and proportion of infants with at least 1 claim, abstracted medical record, and confirmed diagnosis falling in the ICD-9 categories that had an ESS prompting chart review and blinded adjudication

	Montelukast cohort		ICS cohort		Reference cohort no. (%)
	First-trimester exposure, no. (%)	Any-trimester exposure, no. (%)	First-trimester exposure, no. (%)	Any-trimester exposure, no. (%)	
Other deformities of limbs (755.xx)	n = 1,187	n = 1,535	n = 2,285	n = 3,918	n = 38,828
Infants with ≥1 claim bearing a 3-digit ICD-9 code for other deformities of limbs	16	16 (1.0)	17	21 (0.5)	251 (0.6)
Infants with a claims profile consistent with 3-digit ICD-9 diagnosis of other deformities of limbs and an abstracted medical record	NA*	13 (0.8)	NA	12 (0.3)	16 (0.04)
Infants with medical record–confirmed 3-digit ICD-9 diagnosis of other deformities of limbs	NA	6 (0.01)	NA	8 (0.2)	5 (0.01)
Infants with medical record–confirmed 3-digit ICD-9 diagnosis of other deformities of limbs and consistent as a limb-reduction defect	NA	0 (0.0)	NA	2 (0.05)	0 (0.0)
Spina bifida (741.xx)	n = 1,140	n = 1,472	n = 2,212	n = 3,773	n = 37,401
Infants with ≥1 claim bearing a 3-digit ICD-9 code for spina bifida	2 (0.2)	3 (0.2)	1 (0.05)	3 (0.1)	14 (0.03)
Infants with a claims profile consistent with 3-digit ICD-9 diagnosis of spina bifida and an abstracted medical record	1 (0.1)	2 (0.1)	0 (0.0)	1 (0.02)	8 (0.02)
Infants with medical record–confirmed 3-digit ICD-9 diagnosis of spina bifida	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	6 (0.02)
Other congenital anomalies of the heart (746.xx)	n = 1,140	n = 1,472	n = 2,212	n = 3,773	n = 10,625
Infants with ≥1 claim bearing a 3-digit ICD-9 code for other congenital anomalies of the heart	14 (1.2)	15 (1.0)	16 (0.7)	25 (0.7)	66 (0.6)
Infants with a claims profile consistent with 3-digit ICD-9 diagnosis of other congenital anomalies of the heart and an abstracted medical record	13 (1.1)	14 (1.0)	8 (0.4)	12 (0.3)	41 (0.4)
Infants with medical record–confirmed 3-digit ICD-9 diagnosis of other congenital anomalies of the heart	3 (0.3)	3 (0.2)	4 (0.2)	5 (0.1)	18 (0.2)
Other congenital anomalies of the circulatory system (747.xx)	n = 1,140	n = 1,472	n = 2,212	n = 3,773	n = 12,622
Infants with ≥1 claim bearing 3-digit ICD-9 code for other congenital anomalies of the circulatory system	31 (2.7)	38 (2.6)	44 (2.0)	64 (1.7)	192 (1.5)
Infants with a claims profile consistent with 3-digit ICD-9 diagnosis of other congenital anomalies of the circulatory system and an abstracted medical record	13 (1.1)	17 (0.2)	16 (0.7)	25 (0.7)	72 (0.6)
Infants with medical record–confirmed 3-digit ICD-9 diagnosis of other congenital anomalies of the circulatory system	3 (0.3)	3 (0.2)	1 (0.05)	3 (0.1)	21 (0.2)
Other congenital anomalies of the digestive system (751.xx)	n = 1,140	n = 1,472	n = 2,212	n = 3,773	n = 19,429
Infants with ≥1 claim bearing 3-digit ICD-9 code for other congenital anomalies of the digestive system	6 (0.5)	8 (0.5)	8 (0.4)	12 (0.3)	41 (0.2)
Infants with a claims profile consistent with 3-digit ICD-9 diagnosis of other congenital anomalies of the digestive system and an abstracted medical record	2 (0.2)	4 (0.3)	7 (0.3)	11 (0.3)	27 (0.1)
Infants with medical record–confirmed 3-digit ICD-9 diagnosis of other congenital anomalies of the digestive system	2 (0.2)	3 (0.2)	3 (0.1)	5 (0.1)	12 (0.1)

*NA, Not available. Accounting for claims profile review and medical chart review was not obtained by trimester of exposure for “Other deformities of limbs (755.xx)”; these reviews were performed (for all infants within each exposure cohort) regardless of trimester of exposure.

we conducted a retrospective insurance claims cohort analysis across more than 50,000 pregnancies. Complete methods are available in the [Methods](#) section in this article’s Online Repository at www.jacionline.org.

We created mutually exclusive cohorts based on hierarchical classification of maternal antiasthma medication exposure during pregnancy that maximized our ability to identify pregnancies with exposure to montelukast:

1. *Montelukast cohort*: at least 1 prescription for montelukast (in addition to any other asthma drugs);
2. *ICS cohort*: at least 1 prescription for an ICS (in addition to any asthma drugs other than montelukast);
3. *Other asthma medications cohort*: prescriptions of any asthma drugs other than montelukast or ICSs;

4. *Asthma diagnosis cohort*: diagnosis of asthma during pregnancy but no asthma medication prescriptions; and
5. *Reference (general population) cohort*: no asthma-related medication prescriptions and no diagnosis of asthma.

Because limb-reduction defects were an event of primary interest in the analysis, we maximized the likelihood to identify these malformations by searching on the higher-level organ-system category of “other congenital anomalies of limbs” (3-digit International Classification of Disease, ninth revision [ICD-9], diagnostic code = 755), which includes congenital anomalies of limbs not associated with limb-reduction defects. Other congenital anomalies were also grouped based on 3-digit ICD-9 codes.

We performed a 2-stage analysis. First, we performed insurance claims surveillance to identify all potential congenital

malformations (not limited to limb defects) in these cohort populations. Each congenital anomaly group (3-digit ICD-9 code) was evaluated by using the event screening score (ESS) to identify those events with claims rates higher in the montelukast cohort than in the reference cohort. Smaller ESSs identified events unlikely of concern; larger values prompted the second stage: medical chart review to confirm diagnoses from claims meeting predefined ESS values. We prespecified that an ESS of 10 or greater would initiate the chart review procedures for limb defects. For all other congenital anomalies with no prior potential signal, an ESS of 20 or greater was prespecified.

Longitudinal claims histories for infants with anomalies meeting the prespecified ESS criteria were reviewed by a single teratologist (J. M. S.) experienced in review of claims data and blinded to cohort status to determine whether the claims were consistent with the diagnostic code. If so, blinded medical records were obtained for independent adjudication by 3 expert teratologists/dysmorphologists (J. M. S., M. J. B., and M. L. C.). If the adjudicators confirmed a malformation, the malformation was further classified by the more specific 4-digit ICD-9 code based on available chart information. For any limb anomalies, the adjudicators also classified each event as similar to or different than the limb-reduction defects identified in postmarketing surveillance.

Mother-infant identification is shown in Fig E1 in this article's Online Repository at www.jacionline.org. Maternal and perinatal information is shown in Table I. In general, compared with the other asthma medication and reference cohorts, a higher proportion of women in the montelukast cohort had health insurance claims for comorbid conditions, multiple asthma medication dispensings, and teratogenic drug dispensings. The montelukast cohort was similar to the ICS cohort in concomitant asthma medications.

The ESS for congenital anomalies of the limbs in the montelukast cohort exceeded the predefined threshold of 10 for first-trimester dispensings (ESS, 176) and for any-trimester dispensings (ESS, 21.7; see Table E1 in this article's Online Repository at www.jacionline.org). There were 2 infants with claims similar to the 6 postmarketing events (see Table E2 in this article's Online Repository at www.jacionline.org). On claims unblinding, it was determined that these 2 infants were in the ICS cohort. The ESS for montelukast also exceeded the predefined threshold of 20 for 4 other non-limb-anomaly codes.

Medical charts were available for review and adjudication for 41 of 62 infants with claims for congenital anomalies of the limbs (see Fig E2 in this article's Online Repository at www.jacionline.org). As expected, the number of adjudicated/confirmed cases of anomalies was considerably lower than the number based simply on health insurance claims data (Table II). The rates of anomalies among the 3 cohorts were generally similar; however, the numbers of confirmed events for each ICD-9 category of congenital anomaly (range, 0-5) were too low to calculate meaningful rates or perform statistical analysis.

In summary, in this retrospective insurance claims cohort study comprising approximately 12 million covered lives and more than 277,000 pregnancies linked to a live-birth outcome, there were no

events similar to the 6 postmarketing surveillance events of limb-reduction defects among the 1535 infants born to mothers in the montelukast cohort. Other anomalies, confirmed by medical chart review with blinded adjudication, were reported at rates that were similar in the montelukast, ICS, and general population cohorts. The conclusion from this study, together with findings from other pregnancy databases, is that there is no epidemiologic evidence to support a causal relationship between montelukast and limb-reduction or other birth defects.

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METHODS

To identify congenital malformations, we assembled 2 retrospective cohorts of women with a live-born delivery: 1 had a diagnosis of asthma or dispensing of an asthma-related medication during the pregnancy, and the other had no dispensings of any asthma-related medication and no diagnosis of asthma in the pregnancy interval. This medical claims analysis was conducted in 2 stages: (1) surveillance of the cohorts to identify all events representing a potential congenital malformation using high sensitivity and (2) a clinical chart review of identified events to confirm diagnoses and thus provide specificity.

Data source

This retrospective cohort study was based on commercial health insurance claims data from the Ingenix National Health Informatics Database, a proprietary research database containing pharmacy and medical claims and enrollment data dating back to 1993 for members of a large, geographically diverse health plan in the United States. For this study, data relating to approximately 14 million subjects with both medical and pharmacy benefit coverage were available. Drug dispensings were identified by using national drug codes on dispensing claims. Diagnoses were identified by using ICD-9 codes on health care service claims. Procedures were identified by using ICD-9 and Current Procedural Terminology procedure codes. These claims data have been used in previous studies of drug exposure during pregnancy and birth outcomes.^{E1,E2}

This study received institutional review board (IRB) approval from the New England IRB and a Waiver of Authorization for patient medical chart abstraction from the Privacy Board of the New England IRB.

Population

A woman was included in the study if she had at least 1 claim for a live-born delivery between January 1, 1998, and June 30, 2005; complete medical and pharmacy benefit coverage; and at least 280 days of continuous health plan enrollment before the date of delivery. If a woman had a delivery more than once during the study period, we evaluated each of her pregnancies. Health insurance claims data for infants born to these women were able to be linked to the mothers' data. Infants were required to be enrolled in the health plan on the date of their delivery and were followed for up to 9 months after delivery or until an enrollment gap of more than 32 days occurred (whichever interval was shorter). Claims for infants who were matched to mothers were assessed for up to 9 months after delivery (Fig E1).

For normal pregnancies, the pregnancy was estimated to begin 280 days before delivery and end on the date of delivery, and the first trimester was defined as 280 to 183 days before delivery. The pregnancy interval was adjusted if there were claims indicating prematurity and multiple infant pregnancies. Therefore if a woman had a claim bearing an ICD-9 diagnostic code related to low birth weight^{E3} or prematurity, the estimated pregnancy began 238 days before delivery (first trimester defined as 238-141 days before delivery). Because multiple-gestation pregnancies often do not go to full term, if a woman had a claim bearing an ICD-9 diagnostic code for multiple gestation or multiple infants associated with the delivery were identified, the estimated pregnancy interval began 252 days before delivery (first trimester defined as 252-155 days before delivery).^{E3,E4} Exposure during the first trimester was defined as a dispensing of a prescribed medication either within the defined interval of days before delivery (as above) or before this interval but with supply in days extending into the interval.

Study cohorts based on antiasthma medications

A hierarchic assignment scheme was used to create mutually exclusive cohorts based on exposure to specific antiasthma medications. Because the objective was to evaluate pregnancy outcomes associated with prenatal exposure to montelukast, the cohort hierarchy was designed to maximize the ability to identify pregnancies with montelukast exposure before

considering other asthma medications. Thus 5 mutually exclusive cohorts of women with live-born deliveries were prespecified:

1. *Montelukast cohort*: Women had at least 1 prescription dispensing for montelukast in the pregnancy interval. These women could also have had dispensings of ICS and other antiasthma drugs.
2. *ICS cohort*: Women had at least 1 prescription dispensing for ICSs in the pregnancy interval. These women could also have had dispensings of other antiasthma drugs, including combinations of ICSs and long-acting β -agonists, but not montelukast.
3. *Other asthma medications cohort*: Women had dispensings of antiasthma drugs other than montelukast or ICSs (eg, short- and long-acting β -agonists, mast cell stabilizers, omalizumab, zafirlukast, or zileuton) during pregnancy. Note that because oral corticosteroids are used to treat many conditions other than asthma, prescriptions for oral corticosteroids were not used to identify or define women as part of any cohort, but exposures to oral corticosteroids were included among all 3 medication-exposed cohorts.
4. *Asthma diagnosis without medication (hereafter referred to as the asthma diagnosis cohort)*: Women had at least 1 claim with an ICD-9 diagnostic code for asthma during pregnancy but no dispensings for any asthma medications.
5. *Reference (general population) cohort*: Women had no dispensings of any asthma-related medication and no diagnosis of asthma in the pregnancy interval. Because the reference cohort provided a potential sample larger than needed for comparisons in this study, this cohort was chosen as a random sample of 50,000 pregnancies that were not identified in the other 4 cohorts. The reference cohort was approximately 25-fold larger than the montelukast cohort.

Demographic characteristics and analysis

Pregnancies were characterized by demographic characteristics, including age and geographic region of the health plan. Maternal asthma medication use was also summarized but was limited to dispensings during the pregnancy period; dispensings that occurred before the first trimester with supply in days extending into the first trimester were not included. We also determined pregnancy characteristics, maternal comorbidities (including those known to commonly require treatment throughout pregnancy), and asthma-related health care, which was defined as the presence of claims for hospitalizations or physician's office visits associated with an ICD-9 diagnostic code for asthma listed as the primary diagnosis. Note that this definition of asthma-related health care differs from the rules that defined the asthma diagnosis cohort, for which the ICD-9 diagnostic code of asthma did not have to be the primary diagnosis. In this descriptive article no formal inferential statistical testing was performed.

Timing of drug exposure

Exposure to medication by trimester was assigned based on the assigned pregnancy intervals described above, date of medication dispensing, and days of drug supply; drug supply was assumed to be used as dispensed. In the 3 medication-exposed cohorts pregnancies were subclassified based on 2 time frames: (1) *first trimester* was defined as exposure during the estimated first trimester of pregnancy (or with ≥ 1 days' supply extending into the estimated pregnancy window), and (2) *any trimester* was defined as exposure at any time during the pregnancy period. For example, a woman with exposure to ICSs in the first trimester but montelukast exposure in the second trimester would be included in the montelukast cohort and classified within this cohort as having exposure that was during "any" trimester but not during the first trimester.

Surveillance analyses

In the health insurance claims database, congenital anomalies were identified from the unvalidated ICD-9 diagnostic codes on the health insurance claims. It should be noted that claims are submitted for reimbursement purposes and thus might not signify a confirmed clinical diagnosis. Calculation

of prevalence rates was prespecified at 3 levels in each cohort: overall congenital anomalies, specific congenital anomalies identified at the level of a 3-digit ICD-9 code (mapping to an organ system), and limb-reduction anomalies (identified by using the 4-digit ICD-9 codes of 755.2, 755.3, and 755.4). Prevalence rates were calculated as the numbers of events per 10,000 live births for each grouped event (ie, for each 3-digit ICD-9 category) in the reference cohort and the montelukast cohort. As noted, limb-reduction defects were an event of primary interest in the analysis, and as such, it was decided to maximize the likelihood to identify these malformations by searching on the higher-level organ-system category of “other congenital anomalies of limbs” (3-digit ICD-9 diagnostic code = 755). It was also understood that screening on all possible limb defects increased the sensitivity of the claims surveillance to detect limb-reduction defects, although at the expense of specificity.

Because the surveillance was seeking only to identify claims for clinical chart review (which would then provide the necessary specificity to the claims identified), conventional hypothesis-testing constructs, such as *P* values, are inappropriate for a surveillance (screening) analysis. Instead, the ESS was defined as the reciprocal of the probability of observing as many or more events as were reported for the montelukast cohort when the event risk is the same as for the reference cohort. This probability was determined from a Bayesian analysis, assuming Poisson distributions, with the same parameter for the event rate in both cohorts and a common exponential for the prior distribution of the event-rate parameter. Smaller ESS values identified circumstances unlikely to be of concern, and larger values identified candidates for follow-up in this screening process. Because screening for limb reduction was the primary focus of this analysis, we prespecified that an ESS of 10 or greater would initiate the calculation of prevalence rates, 95% CIs, and chart review procedures. For all other congenital anomalies, an ESS of 20 or greater would initiate such procedures.

Claims profile and clinical chart selection for review

For each infant in the 3 cohorts with claims that fell within the prespecified criteria for follow-up (either a 3-digit ICD-9 diagnostic code for “other congenital anomalies of limbs” with an ESS ≥ 10 or any other [3-digit] anomaly codes with an ESS ≥ 20), a claims profile was constructed, as follows. Chronological listings were created from medical and pharmacy claims data (from which all protected health information was removed) from birth until the end of enrollment in the health plan. If an infant had claims bearing more than 1 type of diagnostic code of interest, additional claims profiles were created so that the infant’s claims could be reviewed with regard to each specific diagnostic code. These claims profiles were then reviewed by an expert physician (J. M. S) trained in the profile review process and blinded to cohort status. The expert reviewed the claims profile to determine whether the profile was indeed consistent with the specified diagnostic code. If the expert determined that a claims profile was consistent with the diagnostic code, medical records were requested from the provider who had evaluated the child for the malformation, as follows: the expert selected the provider (in many cases the primary care physician) whose records appeared most likely to yield the most relevant information for chart confirmation (ie, a discharge summary or a specialist consultation), medical record abstraction, or both. A second provider was also selected for backup if the medical record from the first provider was not available.

Medical record abstraction for chart review

The medical records of the children identified with congenital defect codes in all cohorts were reviewed and abstracted using standard forms. A trained nurse abstractor, unaware of either the project sponsor or exposure of interest, requested copies of available relevant documents (eg, office visits, consultations, admission history and physical examinations, emergency department visits, hospital discharge summaries, surgical reports, cardiac procedure reports, laboratory results, imaging reports, and autopsy reports) from the identified provider for details pertaining to the diagnosis and potential malformation. In most cases the entire chart was reviewed by the nurse abstractor, and relevant information was photocopied. If copies could not be made, the information in the required reports was transcribed. All copies of documents and transcribed materials were blinded with regard to patient health information and cohort.

Independent adjudication of identified events

The abstracted, blinded medical records were reviewed by a panel of 3 independent physician consultants (teratologists, dysmorphologists, or both [M. L. C., J. M. S., and M. J. B.]) who independently adjudicated each potential malformation before convening to reach consensus. The adjudicators independently reviewed each patient’s copied and abstracted data and determined, based on the medical records, whether the infant had the 3-digit ICD-9 code diagnosis of interest. If yes, each adjudicator then classified the confirmed malformation using a more specific 4-digit ICD-9 diagnostic code. Specifically for limb anomalies, each adjudicator also classified each event as to whether the event was similar to or different than the 6 limb-reduction defects identified in postmarketing surveillance. Any discrepancies in the individual classifications were adjudicated by consensus, and in the event of disagreement, a majority ruling was made.

For each infant with a chart-confirmed congenital malformation of interest, information was collected on cohort, year of birth, sex, 4-digit ICD-9 diagnostic code (determined by the adjudication panel), and mother’s age (in 5-year categories). Also, a chronologic claims listing was constructed by days before infant birth and by trimester of all prenatal dispensings to the mother of asthma drugs and drugs known to have teratogenic potential.^{E5,E6}

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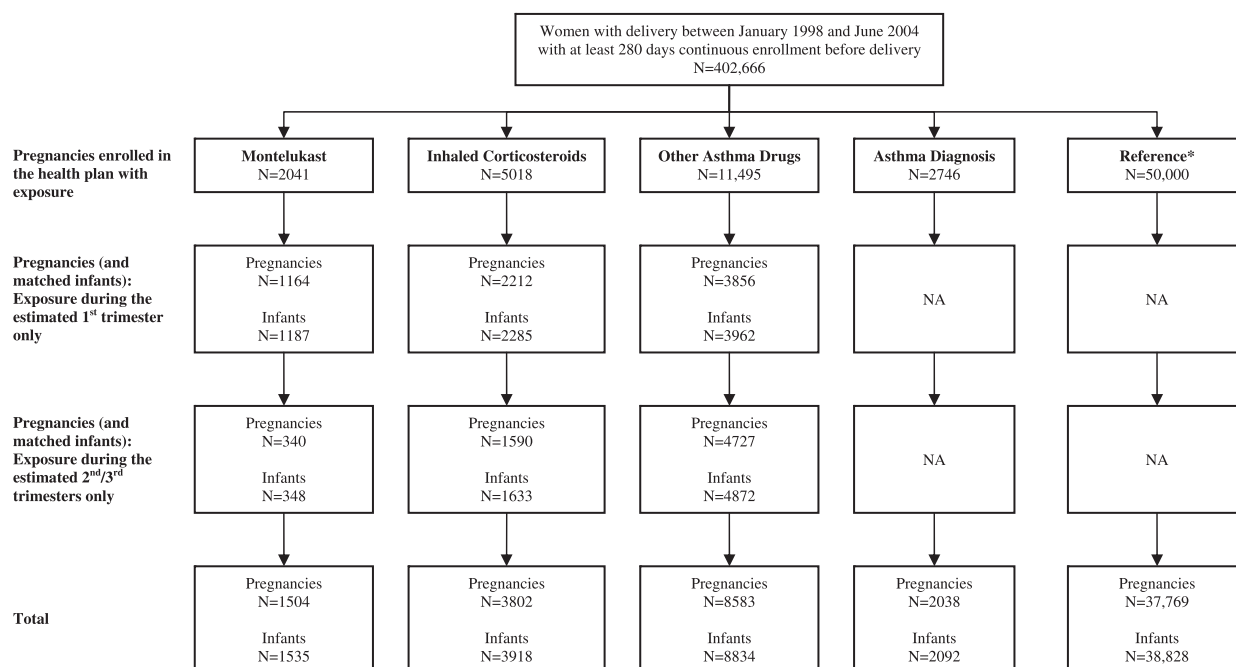


FIG E1. Mother-infant cohort identification. *Randomly selected. NA, Not applicable (patients in the Asthma Diagnosis and Reference cohorts did not have asthma medication exposures, and thus had no trimester exposure classification).

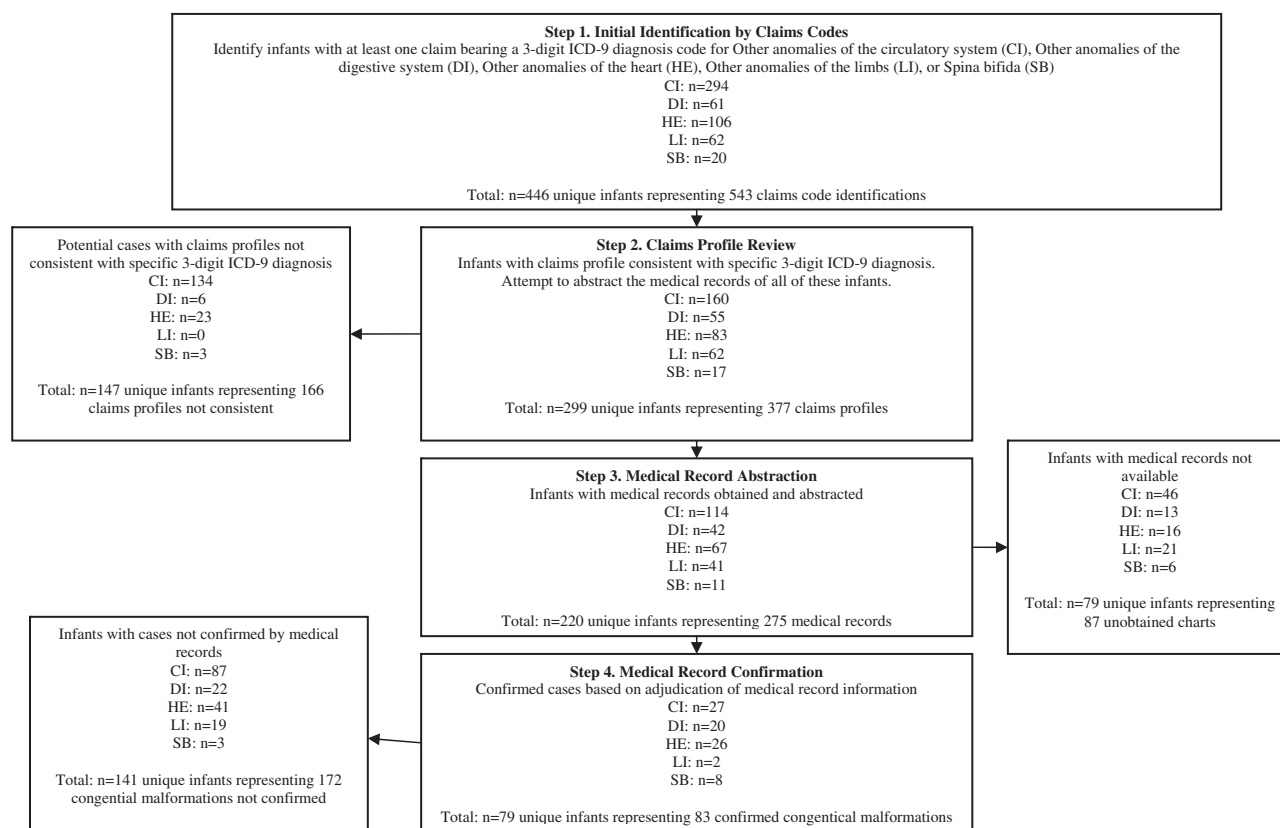


FIG E2. Flowchart of claims profile review, medical record abstraction, and medical record review and adjudication.

TABLE E1. Specific unconfirmed congenital anomaly claims by 3-digit ICD-9 diagnostic code associated with medication dispensing either in the first trimester or in any trimester

		Reference cohort (n = 38,828)		Montelukast cohort (n = 1,187)			ICS cohort (n = 2,285)	
	Event							
ICD-9 group	Description	No.	Rate†	No.	Rate†	ESS*	No.	Rate†
Unconfirmed congenital anomaly claims associated with medication dispensing in first trimester								
740	Anencephalus and similar anomalies	1	0.3	0	0.0	1.0	0	0.0
741	Spina bifida	14	3.6	2	16.8	14.4	1	4.4
742	Other congenital anomalies of the nervous system	108	27.8	2	16.8	1.2	13	56.9
743	Congenital anomalies of the eye	372	95.8	11	92.7	1.7	16	70.0
744	Congenital anomalies of the ear, face, and neck	97	25.0	1	8.4	1.1	5	21.9
745	Bulbus cordis anomalies and anomalies of cardiac septal closure	666	171.5	22	185.3	2.6	44	192.6
746	Other congenital anomalies of the heart	269	69.3	14	117.9	24.2	16	70.0
747	Other congenital anomalies of the circulatory system	570	146.8	31	261.2	479	44	192.6
748	Congenital anomalies of the respiratory system	188	48.4	9	75.8	7.8	11	48.1
749	Cleft palate and cleft lip	56	14.4	3	25.3	4.1	5	21.9
750	Other congenital anomalies of the upper alimentary tract	331	85.2	7	59.0	1.1	15	65.6
751	Other congenital anomalies of the digestive system	79	20.3	6	50.5	27.3	8	35.0
752	Congenital anomalies of the genital organs	668	172.0	25	210.6	5.5	42	183.8
753	Congenital anomalies of the urinary system	163	42.0	4	33.7	1.4	9	39.4
754	Certain congenital musculoskeletal deformities	751	193.4	29	244.3	8.0	63	275.7
755	Other congenital anomalies of limbs	251	64.6	16	134.8	176	17	74.4
756	Other congenital musculoskeletal anomalies	286	73.7	7	59.0	1.3	26	113.8
757	Congenital anomalies of the integument	169	43.5	5	42.1	1.7	7	30.6
758	Chromosomal anomalies	83	21.4	4	33.7	4.0	8	35.0
759	Other and unspecified congenital anomalies	122	31.4	3	25.3	1.4	6	26.3
Unconfirmed congenital anomaly claims associated with medication dispensing in any trimester								
740	Anencephalus and similar anomalies	1	0.3	0	0.0	1.0	0	0.0
741	Spina bifida	14	3.6	3	19.5	53.3	3	7.7
742	Other congenital anomalies of the nervous system	108	27.8	4	26.1	1.6	20	51.0
743	Congenital anomalies of the eye	372	95.8	15	97.7	2.0	36	91.9
744	Congenital anomalies of the ear, face, and neck	97	25.0	3	19.5	1.4	10	25.5
745	Bulbus cordis anomalies and anomalies of cardiac septal closure	666	171.5	28	182.4	2.5	68	173.6
746	Other congenital anomalies of the heart	269	69.3	15	97.7	8.3	25	63.8
747	Other congenital anomalies of the circulatory system	570	146.8	38	247.6	549	65	165.9
748	Congenital anomalies of the respiratory system	188	48.4	9	58.6	3.0	18	45.9
749	Cleft palate and cleft lip	56	14.4	3	19.5	2.6	9	23.0
750	Other congenital anomalies of the upper alimentary tract	331	85.2	12	78.2	1.5	34	86.8
751	Other congenital anomalies of the digestive system	79	20.3	8	52.1	67.6	12	30.6
752	Congenital anomalies of the genital organs	668	172.0	30	195.4	3.7	72	183.8
753	Congenital anomalies of the urinary system	163	42.0	5	32.6	1.3	21	53.6
754	Certain congenital musculoskeletal deformities	751	193.4	35	228.0	5.4	97	247.6
755	Other congenital anomalies of the limbs	251	64.6	16	103.2	21.7	21	53.6
756	Other congenital musculoskeletal anomalies	286	73.7	10	65.1	1.4	42	107.2
757	Congenital anomalies of the integument	169	43.5	7	45.6	2.0	9	23.0
758	Chromosomal anomalies	83	21.4	4	26.1	2.4	9	23.0
759	Other and unspecified congenital anomalies	122	31.4	5	32.6	1.9	13	33.2

Boldface rows indicate anomalies that exceeded the ESS threshold for initiating medical chart review.

*As prespecified for this analysis, the threshold for initiating medical chart review procedures is an ESS of 10 or greater for anomalies of the limbs and 20 or greater for all other anomalies.

†Per 10,000.

TABLE E2. Frequency distributions of medical claims broadly coded as limb anomalies (unconfirmed) based on a 3-digit ICD-9 code of 755 listed by the maximum reported digits of ICD-9 codes

ICD-9 code	Diagnosis description	Montelukast exposed (n = 1,535)	ICS exposed (n = 3,918)	Reference (n = 38,838)
755	OTH CONG LIMB ANOMALY	0	1	0
755.0	POLYDACTYLY	0	1	2
755.00	POLYDACTYLY NOS	1	2	19
755.01	POLYDACTYLY, FINGERS	4	0	25
755.02	POLYDACTYLY, TOES	0	2	7
755.1	SYNDACTYLY	0	0	2
755.10	SYNDACTYLY, MULTIPLE/NOS	0	1	5
755.11	SYNDACTYL FING-NO FUSION	0	0	9
755.12	SYNDACTYL FING W FUSION	0	0	2
755.13	SYNDACTYL TOE-NO FUSION	1	2	6
755.14	SYNDACTYL TOE W FUSION	0	1	1
755.20	REDUC DEFORM UL NOS	0	0	2
755.21	TRANSVERSE DEF ARM	0	0	1
755.27	LONGITUDINAL DEF ULNA	0	0	1
755.29	LONGITUD DEF FINGERS	0	0	2
755.30	REDUCTION DEFORM LEG NOS	0	0	4
755.31	TRANSVERSE DEF LEG	0	0	1
755.33	COMB LONGITUD DEF LEG	0	0	1
755.35	TIBIOFIBULA LONGITUD DEF	0	0	1
755.39	LONGTUD DEF TOES	0	1	1
755.4	REDUCT DEFORM LIMB NOS	0	0	1
755.50	UPPER LIMB ANOMALY NOS	0	0	4
755.51	CONG DEFORMITY-CLAVICLE	0	0	0
755.55	ACROCEPHALOSYNDACTYLY	0	0	4
755.57	MACRODACTYLIA (FINGERS)	0	0	1
755.59	UPPER LIMB ANOMALY NEC	0	1	7
755.6	OTH LOWER LIMB ANOMALIES	0	0	5
755.60	LOWER LIMB ANOMALY NOS	1	2	5
755.62	CONGENITAL COXA VARA	0	0	1
755.63	CONG HIP DEFORMITY NEC	9	9	131
755.64	CONG KNEE DEFORMITY	0	1	2
755.65	MACRODACTYLIA OF TOES	0	0	1
755.66	ANOMALIES OF TOES NEC	0	1	7
755.67	ANOMALIES OF FOOT NEC	0	2	6
755.69	LOWER LIMB ANOMALY NEC	1	0	6
755.8	CONGEN LIMB ANOMALY NEC	0	1	6
755.9	CONGEN LIMB ANOMALY NOS	0	0	3
Total*		16	21	251

The boxed areas represent limb-reduction defects, the anomalies of primary interest.

*Total number of infants with 1 or more ICD-9 codes within 755.xx; infants might have more than 1 code.