

Asthma exacerbations during the first trimester of pregnancy and the risk of congenital malformations among asthmatic women

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Background: Uncontrolled maternal asthma during pregnancy has been hypothesized as a cause of congenital malformation, but literature is scarce on this topic.

Objective: The aim of this study was to investigate whether asthmatic women who had an exacerbation during the first trimester of pregnancy were more at risk of having a baby with a congenital malformation.

Methods: From the linkage of 3 Canadian administrative databases, we reconstructed a cohort of 4344 pregnancies of asthmatic women. Asthma exacerbations were assessed during the first trimester of pregnancy and were defined as a filled prescription for oral corticosteroids, an emergency department visit, or a hospitalization for asthma. Congenital malformations were assessed at birth and during the first year of life of the newborn by using diagnoses recorded in the databases. Generalized estimating equation models were used to estimate adjusted odds ratios of congenital malformations in association with asthma exacerbations.

Results: In the cohort we identified 398 (9.2%) babies with at least 1 malformation and 261 (6.0%) with a major malformation. The crude prevalences of malformations were 12.8% and 8.9%, respectively, for women who had and those who did not have an exacerbation. The adjusted odds ratio for all malformations was 1.48 (95% CI, 1.04-2.09) when comparing women who had and those who did not have an exacerbation. The corresponding figures were 1.32 (95% CI, 0.86-2.04) for major malformations.

Conclusion: Asthma exacerbations during the first trimester of pregnancy were found to significantly increase the risk of a congenital malformation. (J Allergy Clin Immunol 2008;122:1016-1022.)

Key words: Asthma, pregnancy, exacerbation, congenital malformations, cohort study, administrative health databases

Abbreviations used

ED: Emergency department
GEE: Generalized estimating equation
ICD-9: International Classification of Diseases–9th Revision
ISQ: Institut de la statistique du Québec
OR: Odds ratio
RAMQ: Régie de l'assurance-maladie du Québec

Asthma is a frequent chronic disease encountered during pregnancy, affecting between 3% and 12% of pregnant women.¹⁻³ The goal of asthma therapy is to maintain control of asthma symptoms and prevent acute asthma exacerbations.¹ Exacerbations are not unusual events during pregnancy. In a large prospective study, Schatz et al⁴ reported rates of hospitalization for asthma of 2.3% for patients with mild asthma and 26.9% for patients with severe asthma. Other studies have also reported high rates of hospitalization and emergency department (ED) visits for asthma during pregnancy.^{5,6}

Maternal asthma exacerbations during pregnancy have been found to be associated with adverse perinatal outcomes in some studies but not in others.⁷ In a recent meta-analysis Murphy et al⁷ found that women who had an asthma exacerbation during pregnancy were significantly more at risk of having low-birth-weight infants when compared with nonasthmatic women, but no significant association was found with preterm birth and preeclampsia.

This meta-analysis did not report studies that investigated the association between asthma exacerbations during pregnancy and the risk of a congenital malformation. However, we identified 10 studies investigating the association between either markers of asthma exacerbations, such as use of oral corticosteroids, ED visits and hospitalizations for asthma, or level of asthma severity, and the risk of congenital malformations.⁸⁻¹⁷ Seven of these studies compared asthmatic women with and without asthma exacerbations during pregnancy, and none of them reported a statistically significant association, but 5 of them had a small sample size.^{8,9,11,13-16} Three studies compared pregnant asthmatic women with exacerbations with nonasthmatic women,^{10,12,17} and only Bakhireva et al¹⁷ found a significant increased risk of congenital malformation among asthmatic women. In one study pregnant women with different levels of asthma severity were compared with nonasthmatic pregnant women, and no significant associations with congenital malformations were reported.¹² One feature common to these 10 studies is that maternal asthma exacerbations were measured at any point in time during pregnancy, with no attention paid to the first trimester of pregnancy, which

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is recognized to be a critical period of embryogenesis when congenital malformations develop.

To further investigate this association, we performed a large population-based cohort study investigating whether women who had an asthma exacerbation during the first trimester of pregnancy were more at risk of giving birth to infants with a congenital malformation than asthmatic women without an asthma exacerbation during the same period.

METHODS

Source of data

Data for this study were retrieved from 3 administrative databases from the Canadian province of Quebec, Canada. The database of the Régie de l'assurance-maladie du Québec (RAMQ) provides information on medical services dispensed to all residents of Quebec and prescribed medications filled in community pharmacies for residents insured by the RAMQ for their medications, about 43% of the residents of the province.¹⁸ These include the elderly, recipients of social welfare since 1980, and, since January 1997, 1.7 million other adherents, mainly workers and their families who are not covered under a private drug insurance plan at their workplace. MED-ECHO contains information on all hospitalizations occurring in the province, and the Fichier des événements démographiques, administered by the Institut de la statistique du Québec (ISQ), provides information on all births and stillbirths. The RAMQ and MED-ECHO databases have often been used in the past for epidemiologic research in the field of asthma.¹⁹⁻²³ Data recorded in the RAMQ Medication Prescriptions database and the medical diagnosis for asthma recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid.^{24,25} Moreover, some medical diagnoses recorded in the MED-ECHO database have been found to be valid.²⁶

Study design

A cohort of pregnancies from asthmatic women and their children was formed from the linkage of the RAMQ, MED-ECHO, and ISQ databases. This cohort has been described elsewhere and will be briefly described here.²³ The cohort inclusion criteria were as follows: (1) having at least 1 pregnancy ending in a delivery (live birth or still birth) between 1990 and 2000; (2) being 13 to 45 years old at conception; (3) having at least 1 diagnosis of asthma (International Classification of Diseases–9th Revision [ICD-9] code 493) and at least 1 prescription for an asthma medication at any point in time in the prior 2 years or during pregnancy; and (4) being covered by the RAMQ drug insurance plan for at least 1 year before and throughout the duration of the pregnancy. In addition, women taking oral corticosteroids chronically in the year before conception were excluded. The cohort was formed of a maximum of 2 pregnancies per women. For a woman who had 3 pregnancies or more between 1990 and 2000, we kept the 2 first pregnancies. Using the gestational age and date of birth of the offspring recorded in the MED-ECHO and ISQ databases, we retrospectively identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy. The choice of the pregnancy as the unit of analysis allowed us to take into account the fact that a woman could have more than 1 pregnancy during the study period, as well as the social, asthmatic, and medical conditions of the mother, which might vary from one pregnancy to another.

For each pregnancy included in the cohort, we obtained from the RAMQ data on all prescriptions filled (ie, date of filling, name, dose, dosage form, quantity and duration of the prescription, encrypted identification, and specialty of the prescribing physician) and inpatient and ambulatory medical services dispensed (ie, nature of the medical act, date, site of medical practice [outpatient clinic, ED, and hospitalization], diagnosis code, encrypted identification, and specialty of the treating physician) in the year preceding, during, and 1 year after pregnancy. These data were also obtained for the baby during the first year of life. The RAMQ also provided data associated to the date of birth of the mothers and children, receipt of social assistance by the mother, as well as the area of residence of the mother during her pregnancy. MED-ECHO provided data on all maternal acute care hospitalizations, including principal

diagnosis, up to 15 secondary diagnoses, date of admission, and length of hospitalization occurring in the year preceding, during, and after the pregnancy; this is in addition to the length of gestation and birth weight from the delivery hospitalization. With respect to the children, we received hospitalization data for the first year of life. The Fichier des événements démographiques provided data relevant to the level of education of the mother and the parity of the ongoing pregnancy.

An authorization was obtained from the Commission d'accès à l'information du Québec before requesting and linking the information from the RAMQ, MED-ECHO, and ISQ charts. This research project has been approved by the Ethics Committee of Hôpital du Sacré-Coeur de Montréal.

Congenital malformations

All cases of congenital malformation were identified within the cohort by using ICD-9 diagnosis codes specific to congenital malformations (ICD-9 codes 152, 155, 186, 188, 190-192, 197-198, 204-205, 237, 740-759, and 778) obtained from the RAMQ and MED-ECHO databases, either from the mother's or the infant's records (please see Table E1 in the Online Repository at www.jacionline.org for the definition of ICD-9 codes related to congenital malformations). Our list of congenital malformations was compared with the list provided by the Collaborative Perinatal Group²⁷ and verified by a geneticist from Montreal's Hôpital Ste-Justine for exactness and completeness. An infant was identified as a case if he or she had at least 1 diagnosis of a congenital malformation at birth or during the first year of life recorded in the databases.

The geneticist also classified the malformations as either minor or major. A congenital malformation was classified as major if it could be life-threatening or cause major cosmetic defects and if there was at least 1 hospitalization related to the malformation during the first year of life. The primary outcome was any congenital malformations, and the secondary outcome was major congenital malformations.

Maternal asthma exacerbations

The primary exposure variable was maternal asthma exacerbations during the first trimester of pregnancy. Based on the criteria used in the Canadian Asthma Consensus Guidelines, asthma exacerbations were defined as a filled prescription of oral corticosteroids, an ED visit for asthma, or a hospitalization for asthma.²⁸ All the aforementioned events occurring during an interval of 15 days were considered a single exacerbation.

Confounding variables

Four categories of variables, including maternal sociodemographic characteristics, maternal chronic conditions, pregnancy-related variables, and asthma-related variables during pregnancy, were considered potential confounding variables. The mother's sociodemographic characteristics included age at conception (≤ 18 , 19-34, and ≥ 35 years), receipt of social assistance during pregnancy or 2 years prior (yes/no), area of residence at delivery (rural/urban), and level of education (≤ 12 , ≥ 13 years, and missing). Maternal chronic conditions included diabetes mellitus (yes/no), epilepsy (yes/no), and use of recognized teratogenic medications during the first trimester of pregnancy (yes/no).²⁹ Diabetes mellitus and epilepsy were identified from either diagnoses or filled prescriptions of related medications 1 year before or during pregnancy by using a specific algorithm that we developed for each condition, details of which are available on request. Pregnancy-related variables included parity (first/second pregnancy or more) and multiple pregnancies (singleton/twins or more). Epilepsy was selected as a predictor because the disease, the medications used to treat the disease, or both have been shown to be associated with congenital malformations.³⁰ Asthma-related variables included the use of inhaled corticosteroids (yes/no), inhaled or oral short-acting β_2 -agonists (0, $>0-3$, or >3 doses per week), and other asthma medications (long-acting β_2 -agonists, theophyllines, cromoglycate, ipratropium bromide, nedocromil, and corticosteroid with formulation other than inhaled or oral) in the first trimester of pregnancy. The severity of asthma before pregnancy was also considered and measured with a validated index

(mild, moderate, or severe asthma) based on the use of asthma medications and acute care for asthma.³¹

Statistical analysis

We first calculated descriptive statistics to define the pregnancies included in the cohort. We then estimated the overall prevalence of all congenital malformations and major malformations separately. We also estimated these prevalences among women who had and those who did not have an asthma exacerbation during the first trimester of pregnancy. In addition, we estimated the crude association between maternal asthma exacerbations and the risk of the 2 outcomes separately.

The association between maternal asthma exacerbations occurring during the first trimester of pregnancy and the risk of congenital malformations was investigated with 2 generalized estimating equation (GEE) models, one for the outcome of “all malformations” and the other for the outcome of “major malformations.” The GEE models can estimate the effect of independent variables (including the main exposure and confounding variables) on several types of outcomes, namely dichotomous outcomes, such as the presence or absence of a congenital malformation with a logit function, and take into account the fact that a woman could contribute more than 1 pregnancy to the analysis by estimating the correlation between consecutive pregnancies.³² Two logistic regression models were used to assess the same associations among women who did not fill a prescription for an oral corticosteroid during the entire pregnancy. These models were restricted to 1 pregnancy per woman because including more than 1 pregnancy per woman led to GEE models that did not converge. These secondary analyses were undertaken to eliminate the contribution of oral corticosteroids into the association because these medications have been found in several studies to be associated with congenital malformations.³³⁻³⁵

The best models were found by using a backward selection strategy, keeping in the model only covariates that were found to act as a confounder (ie, if the odds ratio [OR] associated with exacerbations changed when the covariate was removed from the model) or those that were significantly associated with the outcome ($P < .05$).³⁶

RESULTS

The cohort was formed of 4344 pregnancies from 3477 asthmatic women; 867 (24.9%) women contributed 2 pregnancies. Among women with 2 pregnancies, 12 had an exacerbation in the first trimester of both pregnancies, 95 had an exacerbation in the first trimester of only 1 pregnancy, and 760 did not have an exacerbation in the first trimester of both pregnancies. In Table I we present the distribution of the congenital malformations identified in the cohort. We identified 495 congenital malformations in 398 infants (prevalence, 9.2%; 95% CI, 8.3-10.0) and 261 cases of major malformations (prevalence, 6.0%; 95% CI, 5.3-6.7). The most frequent malformations were musculoskeletal, followed by cardiac.

The characteristics of the women included in the cohort are presented in Table II. The majority of women were aged between 19 and 34 years at conception, received social assistance during pregnancy, had 12 years or less of education, were living in an urban area, and were primigravida. Less than 3% of the women used a recognized teratogenic medication, whereas 40% of them used inhaled corticosteroids and 35% used more than 3 doses of short-acting inhaled β_2 -agonists per week on average during the first trimester of pregnancy. In the year before pregnancy, 23% were classified as having moderate-to-severe asthma.

In the cohort we identified 321 (7.4%) pregnancies in which the woman had an asthma exacerbation during the first trimester, and in 171 of the exacerbations, the woman filled a prescription for oral corticosteroids (Table III). The prevalence of congenital

TABLE I. Distribution of congenital malformations

	All malformations		Major malformations	
	No.	Percentage	No.	Percentage
Cardiac	87	17.6	74	28.2
Circulatory system	30	6.1	20	7.6
Respiratory system	13	2.6	7	2.7
Nervous system	26	5.3	25	9.5
Digestive system	34	6.9	21	8.0
Urinary system	23	4.7	19	7.3
Eye, ear, face, and neck	37	7.5	19	7.3
Cleft palate and cleft lip	19	3.8	19	7.3
Spina bifida	11	2.2	5	1.9
Genital organs	46	9.3	6	2.3
Musculoskeletal	94	19.0	31	11.8
Limbs	16	3.2	1	0.4
Chromosomal	2	0.4	2	0.8
Integument	11	2.2	7	2.7
Other	46	9.3	6	2.3
Totals*	495	100.00	262	100.00

*The total exceeds the number of cases (398) because an infant might have had more than 1 malformation.

malformations was higher in pregnancies with at least 1 asthma exacerbation: we found crude ORs of 1.50 (95% CI, 1.06-2.12) for all malformations and 1.36 (95% CI, 0.88-2.08) for major malformations.

In Table IV we present the adjusted ORs found in the GEE models to investigate the association between maternal asthma exacerbations during the first trimester of pregnancy and congenital malformations. We found that maternal asthma exacerbations were significantly associated with an increased risk of congenital malformation (OR, 1.48; 95% CI, 1.04-2.09). Maternal asthma exacerbations were also associated with an increased risk of major malformations, but this association did not reach statistical significance. The GEE models also revealed that a lower level of education, multiple pregnancy, and maternal epilepsy were highly associated with an increased risk of congenital malformations.

We also performed analyses among pregnant women who did not fill a prescription for oral corticosteroids during the entire pregnancy. This subcohort of nonusers of oral corticosteroids included 3062 pregnancies (only 1 pregnancy per woman): 116 (3.8%) of them had an exacerbation during the first trimester, and 2946 (96.2%) did not. Among women who had and those who did not have an exacerbation, 15 (12.9%) and 253 (8.6%) had a baby with a congenital malformation, and 11 (9.5%) and 158 (5.4%) had a baby with a major malformation. In this subcohort analysis, we found that maternal asthma exacerbations during the first trimester were significantly associated with a 2-fold increased risk of having a baby with a major malformation (OR, 1.95; 95% CI, 1.03-3.72). A similar association was present for all malformations, but the OR was not found to be statistically significant (OR, 1.63; 95% CI, 0.93-2.85).

DISCUSSION

The results of this study show an increased risk of congenital malformations among babies born to women who had an asthma exacerbation during the first trimester of their pregnancy. The increased risk of a major malformation seems even higher among

TABLE II. Characteristics of women included in the study cohort

	No. (%)
No. of pregnancies	4344 (100.0)
Sociodemographics	
Age at conception (y)	
≤18	715 (16.5)
19-34	3368 (77.5)
≥35	261 (6.0)
Receipt of social assistance during pregnancy or prior 2 years	3914 (90.1)
Level of education at conception (y)	
≤12	3498 (80.5)
≥13	590 (13.6)
Missing	256 (5.9)
Urban area of residence at delivery	3575 (82.3)
Pregnancy-related variables	
First pregnancy	2532 (58.3)
Multiple pregnancy	54 (1.2)
Maternal chronic conditions	
Diabetes mellitus	92 (2.1)
Epilepsy	38 (0.9)
First-trimester use of teratogenic medications	105 (2.4)
Asthma-related variables during the first trimester	
Use of inhaled corticosteroids	1731 (39.8)
Use of short-acting β_2 -agonists (doses per week)	
0	1487 (34.2)
>0-3	1336 (30.8)
>3	1521 (35.0)
Use of leukotriene receptor antagonists	11 (0.25)
Use of other asthma medications	276 (6.4)
Asthma severity before pregnancy	
Mild	3353 (77.2)
Moderate	698 (16.1)
Severe	291 (6.7)

women who did not fill any prescriptions for oral corticosteroids during pregnancy, with a 2-fold increase for women with an exacerbation during the first trimester.

Our study is the first that has focused on the effect of maternal asthma exacerbations occurring during the first trimester of pregnancy, which is recognized as the most critical period for congenital malformations. Uncontrolled asthma and exacerbations are potentially dangerous to the fetus because they can provoke maternal hypoxia combined with respiratory alkalosis, which in turn can decrease the placental blood flow.^{14,37,38} Decreased fetal blood oxygen could result in abnormal growth and development of the fetus.^{14,37-39} Indeed, there is increasing evidence that the oxygen supply to the fetus in the first trimester is tightly controlled and that hypoxia causes an abnormal development of the fetus.⁴⁰ Moreover, maternal hypoxia has been found to be associated with an increased risk of cleft lip and palate in mice.⁴¹

Other studies investigating this topic have assessed asthma exacerbations (or asthma control or severity) during the entire pregnancy. Among the 10 studies⁸⁻¹⁷ that we found in the literature, 3 compared women with uncontrolled or severe asthma with nonasthmatic women,^{10,12,17} and one of these found a significantly increased risk of congenital malformation among asthmatic pregnant women.¹⁷ In this study the prevalence of a major congenital malformation was found to be higher among 103 (3.9%) women using only short-acting inhaled β_2 -agonists, 438 (4.1%) women using inhaled but not oral corticosteroids,

and 113 (2.7%) women using oral corticosteroids than among 303 (0.3%) nonasthmatic pregnant women ($P < .05$).¹⁷ However, it is worth noting that the prevalence of congenital malformations among the nonasthmatic women was unexpectedly low and that the prevalence was found to be lower among the oral corticosteroid group than among the other groups of patients using asthma medications. Among the other 7 studies, 6 had a limited statistical power, with 4 cases of congenital malformations or less within their group of pregnant women with uncontrolled or severe asthma,^{8,9,11,13,14,16} and one had a larger sample size.¹⁵ The larger study, a prospective cohort study published by Schatz et al,¹⁵ compared 130 asthmatic women who used oral corticosteroids, 167 women who used inhaled or intranasal corticosteroids, and 527 women who did not use steroids during pregnancy and found a prevalence of major congenital malformations of 7.0%, 5.4%, and 4.9%, respectively. A test of trend revealed no significant differences among these 3 groups.

The fact that we assessed asthma exacerbations during the first trimester whereas all other studies considered the entire pregnancy to assess an asthma exacerbation or control might explain, at least in part, the differences between our results and those of others. Other methodological issues, such as our time frame of 1 year after birth to identify malformations, the consideration of several potential confounders in the analysis, and the use of pregnant asthmatic women with no exacerbations as the reference category might have also contributed to the observed differences between our results and those of others.

Oral corticosteroids have been found to be associated with an increased risk of congenital malformations and, more specifically, cleft lip, cleft palate, or both.³³⁻³⁵ To try to disentangle the effect of the medication from the effect of exacerbations, we performed an analysis excluding pregnant women who had a claim for these medications during pregnancy. This analysis revealed that women who had an asthma exacerbation (ie, had an ED visit or a hospitalization for asthma during the first trimester of pregnancy) but who did not fill a prescription for oral corticosteroids were 2 times more likely to have a baby with a major congenital malformation than women who did not have an exacerbation. These women might have taken more time to control their exacerbation, or their exacerbation might have deteriorated because of the lack of treatment with oral corticosteroids, and this longer or more intense period of time with uncontrolled asthma might have contributed to the increased risk of major congenital malformations. Having said that, it is important to mention that a woman might not have filled a prescription for oral corticosteroids during the pregnancy but have taken these medications for a very short period of time during a hospital stay. The RAMQ database does provide information about medications filled at community pharmacies but not about medications taken in the hospital. However, this phenomenon should be marginal because oral corticosteroids are usually prescribed for at least 7 days for an exacerbation requiring acute care,¹ and hospitalization for asthma usually lasts for 3 days or less, and patients will have to fill a prescription at the community pharmacy to complete their treatment. Nevertheless, and if present, this exposure misclassification could have led to an overestimation of the effect of asthma exacerbations on the risk of a congenital malformation because oral corticosteroid use during pregnancy is associated with an increased risk of congenital malformation.

The results of this study should be interpreted in light of the following weaknesses. First, the use of medications is based on

TABLE III. Prevalence of congenital malformations as a function of maternal asthma exacerbations during the first trimester of pregnancy

	No. (%)	All malformations n (%)	Major malformations n (%)
Exacerbation*			
Yes	321 (7.4)	41 (12.8)	25 (7.8)
No	4023 (92.6)	357 (8.9)	236 (5.9)
Oral corticosteroids			
Yes	171 (3.9)	20 (11.7)	12 (7.0)
No	4173 (96.1)	378 (9.1)	249 (6.0)
ED visit or hospitalization for asthma			
Yes	260 (6.0)	30 (11.5)	20 (7.7)
No	4084 (94.0)	368 (9.0)	241 (5.9)

*An asthma exacerbation is defined as a filled prescription of oral corticosteroids, an ED visit, or a hospitalization for asthma. Any of these 3 events occurring within 15 days is counted as 1 exacerbation.

TABLE IV. Adjusted ORs of congenital malformation in association with maternal asthma exacerbations during the first trimester of pregnancy

	All malformations		Major malformations	
	Adjusted OR	95% CI	Adjusted OR	95% CI
Exacerbation during the first trimester (yes/no)	1.48	1.04–2.09	1.32	0.86–2.04
Level of education				
≤12	Reference		Reference	
≥13	0.70	0.5–0.98	0.57	0.39–0.89
Missing	0.49	0.27–0.86	0.52	0.26–1.02
Multiple pregnancies (yes/no)	3.92	2.12–7.22	4.62	2.38–8.96
Epilepsy (yes/no)	2.96	1.38–6.35	4.80	2.22–10.34

medication claims, and this might not exactly reflect actual use. Second, cases of congenital malformations were identified by using diagnoses recorded in the administrative databases and have not been formally validated, but there is no reason to believe that the outcome misclassification would be differential in terms of the primary exposure (eg, maternal asthma exacerbations). Third, because of the nature of our observational design and the fact that a large proportion of congenital malformations are of unknown origin, we cannot completely rule out the possibility of residual confounding. Fourth, the cohort is underrepresented in terms of women with high socioeconomic status, and this might limit the generalizability of the study results if the socioeconomic status is an effect modifier. However, we think that this is unlikely because the association between asthma exacerbations and congenital malformations is believed to be physiologic in nature. On the other hand, having a more homogenous study population would increase the internal validity of the study if the socioeconomic status is a confounder. Moreover, it is also worth noting that a very large proportion of our study cohort was formed of women with mild asthma. This is representative of the distribution of asthma severity in a general population, but it might have contributed to underestimation of the effect of asthma exacerbations when compared with the effect that would be found among a sample of women with severe asthma. Because of the sample size limitation, we were unable to stratify the analysis by the level of asthma severity. Our study also has several strengths, such as its large sample size, allowing the assessment of the exposure during the first trimester; data on prescribed medications that have been collected prospectively and independently of the outcome; the absence of bias as a result of patient recall; and

the use of recognized and objective markers of asthma exacerbations.^{42–45}

In conclusion, our study showed a 50% increased risk of congenital malformations for women who had an asthma exacerbation during the first trimester of pregnancy. With the data at hand, we cannot claim that this association is causal because a residual confounding might be present, and part of the observed association might be due to the use of oral corticosteroids. However, this study adds evidence to the necessity of keeping asthma under control during pregnancy to avoid exacerbations. Because recent data are reassuring about the safety of inhaled corticosteroids during pregnancy,²³ health professionals should encourage pregnant women to continue their treatment at recommended doses once they know that they are pregnant to control their asthma symptoms, thus avoiding exacerbations and the need for oral corticosteroids.

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Clinical implications: Health professionals should encourage pregnant asthmatic women to continue their controller therapy to control their asthma symptoms, avoid exacerbations, and reduce the risk of congenital malformations.

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TABLE E1. Congenital malformations

ICD-9 code	Definition
152	Malignant neoplasm of small intestine, including duodenum
155	Malignant neoplasm of liver and intrahepatic bile ducts
186	Malignant neoplasm of testis
188	Malignant neoplasm of bladder
190	Malignant neoplasm of eye
191	Malignant neoplasm of brain
192	Malignant neoplasm of other and unspecified parts of nervous system
197	Secondary malignant neoplasm of respiratory and digestive systems
198	Secondary malignant neoplasm of other specified sites
204	Lymphoid leukemia
205	Myeloid leukemia
237	Neoplasm on uncertain behavior of endocrine glands and nervous system
740	Anencephalus and similar anomalies
741	Spina bifida
742	Other congenital anomalies of nervous system
743	Congenital anomalies of eye
744	Congenital anomalies of ear, face, and neck
745	Bulbus cordis anomalies and anomalies of cardiac septal closure
746	Other congenital anomalies of heart
747	Other congenital anomalies of circulatory system
748	Congenital anomalies of respiratory system
749	Cleft palate and cleft lip
750	Other congenital anomalies of upper alimentary tract
751	Other congenital anomalies of digestive system
752	Congenital anomalies of genital organs
753	Congenital anomalies of urinary system
754	Certain congenital musculoskeletal deformities
755	Other congenital anomalies of limbs
756	Other congenital musculoskeletal anomalies
757	Congenital anomalies of the integument
758	Chromosomal anomalies
759	Other and unspecified congenital anomalies
778	Conditions involving the integument and temperature regulation of fetus and newborn