Systematic Review of the Safety of Regular Preventive Asthma Medications During Pregnancy

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Systematic Review of the Safety of Regular Preventive Asthma Medications During Pregnancy

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OBJECTIVE: To review the safety of regular preventive asthma medications during pregnancy.

DATA SOURCES: The following databases were searched from inception to February 2011: Ovid MEDLINE, PubMed, Cochrane Library, EMBASE and CINAHL Plus.

STUDY SELECTION AND DATA EXTRACTION: The search was limited to human studies published in the English language. Titles of all articles were screened for relevance. Abstracts of relevant articles were scrutinized to confirm relevance before obtaining full text.

DATA SYNTHESIS: Selected articles were read by 2 authors and the accuracy of the data extracted was confirmed.

RESULTS: Thirty-three articles were included in the final review. Small sample size, missing data, inadequate control for confounding factors, and poor documentation of dosage range were common limitations of the studies reviewed. The use of inhaled corticosteroids, cromolyns, and long-acting β_2 agonists during pregnancy was not associated with any particular adverse event, although the fluticasone/salmeterol combination has been associated with poor outcomes in postmarketing studies. Congenital malformations have been reported with leukotriene receptor antagonist exposure during pregnancy, but those women also had exposure to other medications, including oral corticosteroids.

CONCLUSIONS: Some negative outcomes of preventive asthma medications have been reported, although their direct link with medication use is inconclusive. Selection of preventive medications for asthma management during pregnancy should be based on an assessment of the risks and benefits of medication use versus the risks of poorly controlled asthma.

KEY WORDS: asthma, medication safety, neonatology, obstetrics, pregnancy.

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Asthma is a common condition reported during pregnancy internationally.[1] The following asthma management guidelines have highlighted the importance of optimizing the use of asthma medications during pregnancy: American College of Obstetricians and Gynecologists (ACOG) and American College of Allergy, Asthma and Immunology (ACAAI)[2]; British Thoracic Society (BTS)[3]; Global Initiative for Asthma (GINA)[4]; National Asthma Council of Australia (NAC)[5]; and National Heart, Lung and Blood Institute (NHLBI).[6,7]

Poorly controlled asthma can lead to an increased risk of preterm birth, low birth weight, cesarean section, intrauterine fetal death, intrauterine growth restriction, congenital malformations (eg, ventricular and atrial septal malformation, spina bifida), small for gestational age (SGA), preeclampsia, chorioamnionitis, low Apgar scores, and gestational diabetes.[8-12] Fetal hypoxia, also a result of poorly controlled asthma during pregnancy, can lead to severe risks of neonatal respiratory difficulties, fetal brain ischemia, and cerebral palsy.[13] Children exposed to uncontrolled maternal asthma during gestation have also been shown to develop asthma later in life.[14] Moreover, fetal growth restriction has been associated with the child developing ischemic heart disease, hypertension, and type 2 diabetes in adulthood.[15] Conversely, well-controlled maternal asthma has been shown to decrease the risks of congenital malformations and birth and delivery complications.[16] An acute asthma attack during pregnancy, if promptly treated, is unlikely to have a serious effect on pregnancy, delivery, or the health of a newborn infant.[17]

Upon realizing they are pregnant, some women may choose to discontinue or decrease their asthma therapy for fear of harm associated with their asthma medications.

Author information provided at end of text.

Chambers[18] found that 39% (n = 501) of women discontinued or reduced their asthma medications during pregnancy. In one study, nearly two thirds of pregnant women with asthma were found to be undertreated for 3 or more months of pregnancy.[18] These subtherapeutic regimens could be explained by prescribers heavily relying on the Food and Drug Administration (FDA) pregnancy categories[19] when prescribing asthma medications during pregnancy.[20] The possibility of fetal harm appears to be remote with the FDA-designated category A, as controlled studies have failed to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters). Risk of the use of category B and C drugs is debatable, as there are limited controlled studies confirming their safety in pregnancy, although category C drugs have shown adverse fetal outcomes in animal studies. Because of evidence of negative fetal outcomes, category D and category X drugs are not recommended in pregnancy. Heavy reliance on these FDA pregnancy risk categories may cause a prescriber's reluctance to weigh risks versus benefits of drugs for asthma treatment.[20]

Previous reviews on this topic are outdated or have focused on specific outcomes.[21-24] Our objective was to conduct an updated systematic review of the safety of regular preventive asthma medications during pregnancy to guide optimal management of asthma during pregnancy.

Data Sources

The following databases were searched from inception to February 2011: Ovid MEDLINE, PubMed, Cochrane Library, EMBASE and CINAHL Plus. The search terms used were pregnan* and asthma*. Further searches were conducted in PubMed and Ovid MEDLINE using the key words pregnan* and foet*/fet* and each of eformoterol, formoterol, salmeterol, budesonide, ciclesonide, beclomethasone, fluticasone, triamcinolone, nedocromil, cromolyn, chromone, montelukast, zafirlukast, leukotriene antagonist, corticosteroid, LTRA, LABA, and ICS. A MeSH search was also conducted in PubMed, using pregnancy and asthma as the key words.

Study Selection and Data Extraction

The searches were limited to human studies published in the English language. Methylxanthines, oral corticosteroids, short-acting β_2 agonists (SABAs), and anticholinergics were not included, as these are not recommended for regular preventive use by asthma guidelines.[2-7]

The steps in the study selection process are summarized in Figure 1 and were performed by 1 author (AL). Data from studies identified in the search were extracted and tabulated separately by one author (AL) according to drug class. Similarities and differences in results were identified and methodologic strengths and limitations of studies were considered. All the articles identified in step 4 were read by a second author (JG), who independently extracted data. Any discrepancies were discussed and consensus was reached.

Data Synthesis

Thirty-three articles were included in the final review; some studies included more than 1 drug class. There were 30 inhaled corticosteroid (ICS) entries,[8,17,25-46] 2 combination therapy entries,[46,47] 7 long-acting β_2 agonist (LABA) entries,[37,39,45,48-51] 5 leukotriene receptor antagonist (LTRA) entries,[37,52-55] and 5 cromolyn entries.[29,37,39,45,50] Study designs included cohort studies (n = 28), randomized controlled trials (n = 2), case-control studies (n = 2), and case series (n = 1).

Inhaled Corticosteroids

Many ICS studies were retrieved (Table 1).

The rates of pregnancy-induced hypertension (17%) and cesarean delivery (30%) were higher in pregnant women hospitalized with asthma exacerbations (n = 72) compared with the general obstetric population (13% and 17%, respectively).[28] Posthospitalization, a 55% reduction in asthma exacerbations and subsequent hospital admissions was observed in women who used inhaled beclomethasone (n = 34) compared to those who did not (n = 31).[28] Furthermore, Wendel et al.[28] have shown very low incidences of perinatal adverse events regardless of beclomethasone use. Dombrowski et al.[30] compared inhaled beclomethasone with oral theophylline and found similar rates of asthma exacerbations and outcomes in the 2 groups; however, doses of beclomethasone were higher than the average dose range used by the general population (100-400 µg/daily). The randomized controlled trial by Silverman et al.[33] showed similar incidences of adverse events in the budesonide group (400 µg/daily) and the placebo group; healthy children were delivered in 81% of all budesonide-exposed pregnancies (n = 196) and 77% for placebo (n = 117). Other studies reported no significant increases in adverse events; Namazy et al.[38] and Kallen et al.[31] reported that the rates of adverse events, such as gastroschisis, oral clefts, cardiac defects (eg, ductus arteriosus), spina bifida, and chromosomal anomalies, were no greater than that expected in the general population. Greenberger and Patterson[26] related their incidence of congenital malformations (2.3%; 45 pregnancies) to the incidence in the general population (1.0-6.5%). Alexander et al.[8] found a statistically significant increased risk of antepartum hemorrhage, as well as pregnancy-induced hypertension and hyperbilirubinemia with steroid use (oral or inhaled).

Unfortunately, comparative studies of ICSs are lacking and no human studies on ciclesonide were found in our

search. Dombrowski et al.[27] found fewer hospital admissions for the triamcinolone group compared to those treated with beclomethasone and a lower trend for low-birthweight infants. Birth weight differences among the 3 groups were not statistically significant. A mean neonatal intensive care stay of 2.7 ± 7.0 days was reported, but it was not stated how many infants were admitted to neonatal intensive care. The authors acknowledged that the small sample size precluded any meaningful analysis.

Comparisons of ICS doses were also not widely studied. However, Blais et al.,[44] in an exposure study including beclomethasone, budesonide, and fluticasone, found that women who used more than 1000 µg/day of ICS (beclomethasone diproprionate-chlorofluorocarbon equivalent) in the first trimester were 63% more likely to have a baby with congenital malformation (musculoskeletal and cardiac malformations being most prominent) than women who used none or up to 1000 µg/day. Conversely, infants of women who used none or up to 1000 µg/day in the first trimester were not at any greater risk of malformation than those of mothers who did not use ICSs. Multiple pregnancies, diabetes mellitus, and receipt of social assistance were risk factors for the outcome, whereas other covariates, such as maternal sociodemographic characteristics, were neither confounders nor risk factors. Women who used high doses of ICSs during the first trimester were older, less likely to have a singleton pregnancy, and less likely to have a chronic disease other than asthma. Women who were using high doses of ICSs were likely to have had more severe and uncontrolled asthma. Many studies did not specify a dosage range; thus, a dosage threshold above which adverse events were more likely to occur was not evident.

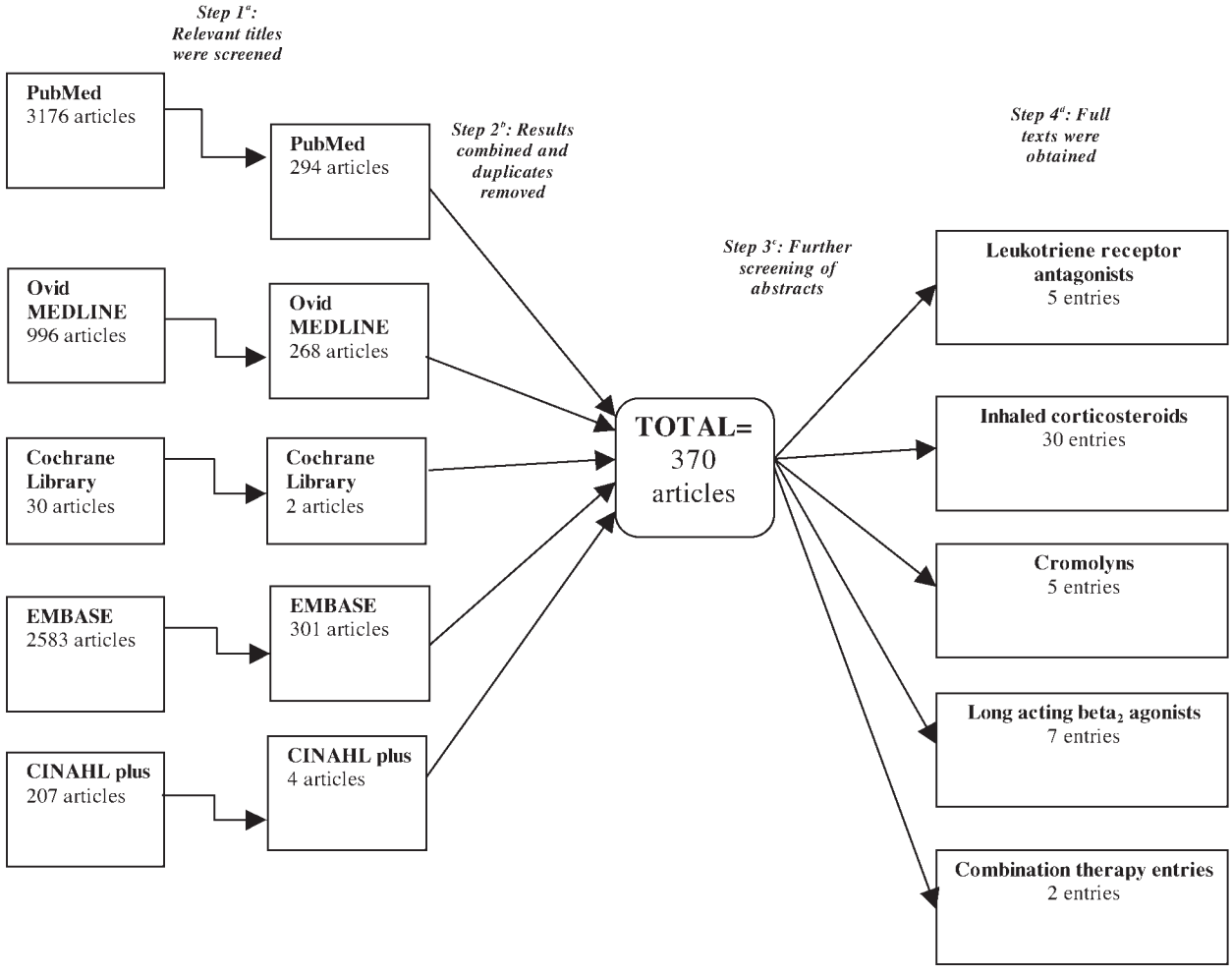

Figure 1. Steps in the study selection process. [a]Articles from each database were imported into a separate EndNote (version 3, Thomson Reuters) library because of the volume; all titles were screened for their relevance. The results from the PubMed MeSH search were combined with the PubMed key word search results and duplicates were removed. Titles were selected if they included specific drug names, class names or key words pertaining to asthma and medications. Review articles and those outside the scope of the topic question were also removed. [b]Selected articles from the various databases were imported and combined into 1 EndNote library and duplicates were removed. [c]Abstracts of relevant articles were scrutinized to confirm relevance and matching to the study inclusion criteria before obtaining their full text. [d]The reference lists of published reviews on the topic were manually searched to ensure that relevant original articles were not missed.

Table 1. Studies on the Safety of ICSs

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Beclomethasone dipropionate (pregnancy risk category C)[19]				
Morrow-Brown (1974)[25]	Cohort	Exposed: asthmatic pregnant women (N = 20)	D: ~450 µg/day; a few pts. required 600 µg/day DF: inhaled (technique checked until satisfactory)	No spontaneous or therapeutic abortions; all women delivered healthy children
Greenberger (1983)[26]	Cohort	Exposed: asthmatic pregnant women (N = 40; 45 pregnancies; 37 also received oral corticosteroids)	D: 168-672 µg/day DF: inhaled	Preeclampsia (n = 1), hypertension (n = 3), spontaneous abortion (n = 3/33), congenital malformation (n = 1) (cardiac malformation); MBW 3233 g; no fetal or maternal deaths; low birth weights (1820-2458 g) with use of higher doses (6-16 puffs/day)
Dombrowski (1996)[27]	Cohort	Exposed: asthmatic pregnant women (n = 14) Asthmatic pregnant women using inhaled triamcinolone (n = 15) Asthmatic pregnant women using oral theophylline (n = 25)	D: NR DF: inhaled	No incidence of anomalies, grade 3 or 4 intraventricular hemorrhages, or sepsis; MBW 2798 ± 759 g, mean gestational age 38.0 ± 3.1.wk, mean Apgar scores at 5 min 8.6 ± 0.9, mean cord arterial pH 7.24 ± 0.11, mean neonatal intensive care stay 4.8 ± 9.4 days
Wendel (1996)[28]	Cohort (women hospitalized for asthma exacerbation; within an RCT)	Exposed: asthmatic pregnant women (n = 34) Unexposed: asthmatic pregnant women (n = 31)	D: 4 puffs twice daily (µg/puff NR) DF: inhaled	Cohort did not show increased incidence of preterm delivery, low birth weight, pathologic acidemia (umbilical artery blood pH <7), perinatal mortality
Schatz (1997)[29]	Cohort	Exposed: asthmatic pregnant women (n = 137) Unexposed: nonasthmatic pregnant women (n = 1430)	D: NR DF: inhaled	Preeclampsia (10.9%), preterm delivery (7.8%), low birth weight (4.7%); exposure without concomitant oral corticosteroids not associated with these factors
Dombrowski (2004)[30]	RCT	Asthmatic pregnant women using inhaled beclomethasone and placebo theophylline (n = 194) Asthmatic pregnant women using theophylline and placebo beclomethasone (n = 190)	D: 504 µg/day DF: inhaled	Chorioamnionitis (n = 10), preeclampsia (n = 16), preterm delivery (n = 40), hemorrhage (n = 12), cesarean delivery (n = 30), oligo-hydramnios (n = 7); no significant differences between groups in obstetric outcomes
Namazy (2004)[38]	Cohort	Exposed: asthmatic pregnant women (n = 201 of 396 exposed to ICSs)	D: mostly 92-600 µg/day[a] DF: inhaled	MBW 3421 ± 37.5 g; for all ICSs; low birth weight (<2500 g; 3.3%), preterm delivery (6.1%), congenital malformation (n = 4: gastroschisis, oral cleft, hypospadias, hypoplastic kidney); ICS use not shown to reduce intrauterine growth
Budesonide (pregnancy risk category C)[19]				
Kallen (1999)[31]	Cohort	Infants whose mothers were exposed to inhaled budesonide in early pregnancy (N = 2014)	D: NR DF: inhaled	Congenital malformations: orofacial cleft (n = 4), cardiac defect (n = 16) (includes 2 preterm babies with ductus arteriosus), other structural defects (n = 16, including spina bifida and microcephaly), chromosomal anomaly (n = 5); no increase in general rate of malfor mations over the population rate (3.8% vs 3.5% respectively)
Norjavaara (2003)[32]	Cohort	Asthmatic pregnant women using 1. only budesonide (n = 2968) 2. other antiasthmatic drugs (not inhaled or oral corticosteroids) (n = 7719) 3. oral corticosteroids plus budesonide (n = 103)	D: NR DF: inhaled	Similar rates of stillbirth, multiple birth, MBW, and mean birth length between groups; increased rate of caesarean birth regardless of treat-ment (group 1: 13.1% vs 16.2%, group 2: 13.3% vs 14.7%, group 3: 30.8% vs 21.6% for girls and boys, respectively) vs all women (11.3% for girls vs 12.2% for boys)
Namazy (2004)[38]	Cohort	Exposed, pregnant asthmatic women (n = 43 of 396 who used ICSs)	D: most 92-600 µg/daya DF: inhaled	MBW 3393 ± 69 g; for all ICSs: infants with low birth weight (<2500 g; 3.3%), preterm delivery (6.1%), congenital malformation (n = 4: gastro-schisis, oral cleft, hypospadias, hypoplastic kidney); ICS not shown to reduce intrauterine growth

Silverman (2005)[33]	RCT	Exposed: asthmatic pregnant women (n = 196) Unexposed: asthmatic pregnant women (n = 117)	D: 400 µg/day DF: inhaled	Healthy children delivered in 81% of exposed pregnancies vs 77% of unexposed pregnancies; no increased risk of adverse events: unspecified congenital malformations (3/196 vs 4/117), spontaneous abortion (23/196 vs 11/117), extrauterine pregnancy (4/196 vs 3/117), induced abortion (6/196 vs 6/117), other outcomes (2/196 vs 3/117), hypertension (1/96 vs 2/117)
Clifton (2006)[46]	Cohort	Asthmatic pregnant women using budesonide alone (n = 14), fluticasone alone (n = 18), or fluticasone/salmeterol (n = 9) Pregnant nonasthmatic women (n = 20)	D: 1092.8 µg/day[b] DF: inhaled	No significant differences in gestational age (39.7 vs 40.2 wk), MBW (3824.6 vs 3423.3 g), mean birth length (52.8 vs 51.8 cm), head circumference (35.3 vs 34.2 cm) with budesonide vs nonasthmatic women, respectively
Flunisolide (pregnancy category C)[19]				
Namazy (2004)[38]	Cohort	Exposed: asthmatic pregnant women (n = 25 of 396 exposed to ICSs)	D: most 92-600 µg/day[a] DF: inhaled	MBW 3452 ± 120.3 g; for all ICSs: low birth weight (<2500 g) (3.3%), preterm delivery (6.1%), congenital malformation (n = 4; gastroschisis, oral cleft, hypospadias, hypoplastic kidney; ICSs not shown to reduce intrauterine growth
Fluticasone propionate (pregnancy risk category C)[19]				
Namazy (2004)[38]	Cohort	Exposed: asthmatic pregnant women (n = 132 of 396 exposed to ICSs)	D: most 92-600 µg/day[a] DF: inhaled	(n = 4: gastroschisis, oral cleft, hypospadias, hypoplastic kidney); ICSs not shown to reduce intrauterine growth
Clifton (2006)[46]	Cohort	Pregnant asthmatic women using budesonide alone (n = 14) fluticasone alone (n = 18) fluticasone/salmeterol (n = 9) Nonasthmatic pregnant women (n = 20)	D: 971.05 µg/day[b] DF: inhaled	No significant differences in gestational age (39.6 vs 40.2 wk), MBW (3441.7 vs 3423.3 g), mean birth length (51.6 vs 51.8 cm), head circumference (34.9 vs 34.2 cm) with fluticasone vs nonasthmatic women, respectively
Choi (2007)[34]	Case series	Exposed: pregnant women with respiratory illness (N = 12)	D: 1-2 puffs/day (µg/puff NR) DF: inhaled/intranasal	Abortions (n = 3; 1 spontaneous, 2 requested); no evidence of major congenital malformations or neurodevelopmental delay at birth or 1 wk postdelivery; 3 premature births (34^{+3} wk [twins] and 36^{+4} wk)
Perrio (2007)[35]	Cohort	Exposed: asthmatic pregnant women (N = 55)	D: 50-250 µg DF: inhaled	Spontaneous abortion (n = 5), elective abortion (n = 2), congenital abnormalities associated with extreme prematurity (n = 1), ventricular septal defect with neonatal jaundice and clicky hips (n = 1), bilateral hydroceles (n = 1), clicky hips (n = 1), positional talipes (n = 1), prune belly syndrome (n = 1)
Triamcinolone acetonide (pregnancy risk category C)[19]				
Dombrowski (1996)[30]	Cohort	Exposed: asthmatic pregnant women (n = 15) Asthmatic pregnant women using inhaled beclomethasone (n = 14) Asthmatic pregnant women using oral theophylline (n = 25)	D: NR DF: inhaled	No anomalies, grade 3 or 4 intraventricular hemorrhages, sepsis; MBW 3300 ± 678 g, mean gestational age 39.2 ± 2 wk, mean neonatal intensive care stay 2.7 ± 7 days, mean cord arterial pH 7.3 ± 0.1, mean Apgar 5-min score 8.8 ± 0.9
Namazy (2004)[38]	Cohort	Exposed: asthmatic pregnant women (n = 81 of 396 women exposed to ICSs)	D: most 92-600 µg/day[a] DF: inhaled	MBW 3508 ± 60.1 g; for all ICSs: low birth weight (<2500 g) (3.3%), preterm delivery (6.1%), congenital malformation (n = 4: gastroschisis, oral cleft, hypospadias, hypoplastic kidney); ICSs not shown to reduce intrauterine growth

D = dosage; DF = dosage form; ICSs = inhaled corticosteroids; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; MBW = mean birth weight; NR = not reported; RCT = randomized controlled trial; SABAs = short-acting β_2 agonists.

[a]Average daily dose was expressed in beclomethasone diproprionate-chlorofluorocarbon equivalent using an algorithm developed and used in previous studies and recognized by the Canadian Asthma Consensus Guidelines.

[b]Average daily dose was expressed in budesonide equivalent.

[c]IGF-1 and IGF-2 are polypeptides with a sequence related to insulin, which have mitogenic properties inducing somatic cell growth and proliferation and are required for optimal fetal and placental growth. IGFBP-3 correlates with birth weight and IGFBP-1 correlates inversely with birth weight in term or preterm infants. IGF axis is a major contributor to fetal and placental development.

(continued on page 936)

Table 1. Studies on the Safety of ICSs (continued)

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Inhaled corticosteroids (nonspecific)				
Stenius-Aarniala (1996)[17]	Cohort	Asthmatic pregnant women who had ICS exposure during pregnancy only after an acute episode (n = 177) used ICSs throughout pregnancy (n = 257) started ICSs at various stages during pregnancy, but before any acute episode (n = 70) Healthy nonasthmatic pregnant women (n = 237)	D: beclomethasone 0.05-3 µg, budesonide 0.2-4 µg DF: inhaled	No significant differences among groups in congenital malformations, premature rupture of membranes, length of gestation, premature uterine contractions, premature separation of placenta, Apgar scores, relative birth weight, hypoglycemia, jaundice, admissions to hospital during the first week of life
Alexander (1998)[8]	Cohort	Exposed: pregnant asthmatic women with or without other drugs (n = 139) Asthmatic pregnant women on no drugs (n = 375) Asthmatic pregnant women on β_2 agonists only (n = 303) Unexposed: pregnant, nonasthmatic women (n = 13,709)	D: NR DF: inhaled or oral (not specified)	Outcomes for asthmatic pregnant women: increased risk of antepartum hemorrhage (15.2%, 11.6%, 10.0%, 8.0%), pregnancy-induced hypertension (18.1%, 13.7%, 11.1%, 10.5%), hyperbilirubinemia (16.1%, 8.6%, 8.5%, 8.8%)
Olessen (2001)[36]	Cohort	Exposed: asthmatic pregnant women (n =108) Unexposed: pregnant women who did not purchase prescription drugs (n = 8717); asthma status NR	D: NR DF: inhaled	Mean gestational age 276.3 ± 15.5 days, MBW 3357.0 ± 524.9 g, mean length at birth 51.2 ± 2.5 cm; no significant difference in these variables between exposed vs reference group
Bracken (2003)[37]	Cohort	Exposed: pregnant asthmatic women (n = 176) Unexposed: pregnant nonasthmatic women (n = 2065)	D: NR DF: inhaled	No increased risk of intrauterine growth restriction (5.9% of 136 exposed vs 7.7% of 2065 not exposed); no increased risk of preterm delivery (8.5% of 176 exposed vs 6.7% of 2029 not exposed)
Schatz (2004)[39]	Cohort	Exposed: asthmatic pregnant women (n = 722) Unexposed: pregnant asthmatic women (n = 1401)	D: NR DF: inhaled	Gestational hypertension (11.2%), preterm delivery (16.2%), low birth weight (13%), small for gestational age (7.1%), unspecified major malformations (1.9%); no significant differences between adverse perinatal outcomes and use of ICSs
Bakhireva (2005)[40]	Cohort	1. Exposed: asthmatic pregnant women (n = 438), including fluticasone, beclomethasone, budesonide, triamcinolone, flunisolide 2. Unexposed: nonasthmatic pregnant women (n = 303) 3. Unexposed: asthmatic pregnant women who used only SABAs (n = 103) 4. Unexposed or exposed: asthmatic pregnant women with concomitant systemic corticosteroids (majority, burst therapy) (n = 113)	D: NR DF: inhaled	No significant differences in MBW (3524 vs 3540 g), mean birth length (51.3 vs 51.6 cm), mean head circumference (34.7 vs 34.7 cm) in group 1 vs 2 Significantly low prevalence of major structural anomalies in group 2 (0.3%); however, similar prevalence in groups 1, 3, and 4 (2.7-4.1%)
Martel (2005)[41]	Case-control	Pregnancy-induced hypertension (n = 302) Preeclampsia (n = 165) Matched controls: pregnancy-induced hypertension (n = 3013), preeclampsia (n = 1643)	D: 0 to >500 µg/day[a] DF: inhaled	No significant difference in risk of pregnancy-induced hypertension in cases vs controls 1-200 µg/day: 35% vs 33% 201-500 µg/day: 10% vs 9% >500 µg/day: 5% vs 5% No significant difference in risk of preeclampsia in cases vs controls 1-200 µg/day: 35% vs 30% 201-500 µg/day: 12% vs 9% >500 µg/day: 5% vs 5%
Blais (2007)[43]	Cohort	Asthmatic pregnant women (n = 4561) using 1. no ICSs (n = 2740) 2. >0-500 µg/day ICSs (n = 1582) 3. >500-1000 µg/day ICSs (n = 167) 4. >1000 µg/day ICSs (n = 72)	D: 0 to >1000 µg/day[a] DF: inhaled	Moderate doses (>500-1000 µg/day) during first trimester significantly associated with a 59% reduction in risk of all congenital malformations vs no ICS use; no increased risk of all malformations/major malformations with first-trimester use of ICSs (groups 1-4: 9.4%/6% vs 9.0%/6.4% vs 5.4%/3.6% vs 12.5%/9.7)

Tata (2008)[45]	Case-control	Children with ≥1 reported major malformation (n = 5124); 220 mothers exposed to ICSs Children with no malformations, matched by year of birth, general practice and singleton or twin delivery (n = 30,053); 1209 mothers exposed to ICSs	D: NR DF: inhaled	No increased risk of congenital malformations (4.3% cases vs 4.0% controls)
Blais (2009)[44]	Cohort	Exposed: asthmatic pregnant women using 1. no ICSs (n = 8734) 2. >0 to ≤1000 µg/day of ICSs (n = 4392) 3. >1000 µg/day of ICSs (n = 154)	D: 0 to >1000 µg/day[a] DF: inhaled	Group 3 not 63% more at risk of delivering an infant with a malformation vs group 2; group 2 not more at risk of delivering an infant with a malformation vs group 1; crude prevalence of all malformations/major malformations (groups 1-3): 9.6%/5.9% vs 9.0%/5.7% vs 14.3%/9.7%
Clifton (2010)[42]	Cohort	Exposed: asthmatic pregnant women (n = 107) Unexposed: nonasthmatic women (n = 38)	D: NR DF: inhaled	ICSs did not affect cord plasma IGF-1, IGF-2, IGFBP-1, IGFBP-3, IGF axis[c]

D = dosage; DF = dosage form; ICSs = inhaled corticosteroids; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; MBW = mean birth weight; NR = not reported; RCT = randomized controlled trial; SABAs = short-acting β_2 agonists.

[a]Average daily dose was expressed in beclomethasone diproprionate-chlorofluorocarbon equivalent using an algorithm developed and used in previous studies and recognized by the Canadian Asthma Consensus Guidelines.

[b]Average daily dose was expressed in budesonide equivalent.

[c]IGF-1 and IGF-2 are polypeptides with a sequence related to insulin, which have mitogenic properties inducing somatic cell growth and proliferation and are required for optimal fetal and placental growth. IGFBP-3 correlates with birth weight and IGFBP-1 correlates inversely with birth weight in term or preterm infants. IGF axis is a major contributor to fetal and placental development.

Asthma severity can be a serious confounding factor, as it is difficult to establish whether the adverse events are attributable to the medications or uncontrolled asthma. Some studies attempted to control for asthma severity.[17,26,28,30,35,37,40-42,46] Analyses in both the mild and moderate-severe asthma groups indicated no effect on fetal growth.[46] Greenberger and Patterson[26] evaluated pregnant women with severe asthma who were exposed to beclomethasone and found only 1 infant with a cardiac malformation, including a double ventricular septal defect, patent ductus arteriosus, and subaortic stenosis. The infant's mother had schizophrenia, asthma and diabetes, and was taking a cocktail of chronic long-term medications, including antipsychotics. Namazy et al.[38] found a nonsignificant trend of increasing incidence of SGA infants with increasing doses of ICS after controlling for factors such as race, smoking, and acute asthma episodes. Choi et al.[34] stated that during pregnancy, none of their 12 ICS-exposed participants experienced uncontrolled asthma.

The relationship between gestational exposure time and adverse events has not been explored in depth.[29,31,32,34,35,43,44,47] Perrio et al.[35] found that 17 of 18 babies exposed to fluticasone in the first trimester were born at term. One baby had a congenital abnormality associated with extreme prematurity; another had a ventricular septal defect, clicky hips, and neonatal jaundice, which was attributed to the mother's antibodies; and 3 babies were born with minor congenital abnormalities. All babies exposed to fluticasone in the second or third trimester were born at full term; 1 baby was born with prune belly syndrome (time of exposure uncertain). Norjavaara et al.[32] found no significant differences in birth weight, length, and gestational age when comparing budesonide exposure in early pregnancy with any time during pregnancy.

Systemic absorption of ICSs following inhalation is generally minimal. Inhaled budesonide has an estimated lung bioavailability of 34% of the inhaled dose and, once absorbed, it becomes a weak systemic steroid.[56] Triamcinolone, fluticasone, ciclesonide, and beclomethasone have low to undetectable plasma concentrations when inhaled.[57] It is uncertain the extent to which these drugs can cause adverse events, considering such low systemic absorption after inhalation.

Oral corticosteroid burst therapy was administered in most studies, which would have added to the corticosteroid concentrations and increased the likelihood of an adverse event. In the study by Namazy et al.,[38] at least 1 course of oral corticosteroids for acute asthma episodes was required by 31.1% of women in the ICS-exposed group (n = 123), of whom 10.6% (n = 13) had SGA babies.

Most of the retrieved ICS studies had small sample sizes and did not control for other contributing risk factors. More adequately powered studies showing a strong correlation between ICS use and an adverse event would be needed before their use during pregnancy should be discouraged.

Combination Therapies

Limited information is available on combination therapies (Table 2). No studies were retrieved on the eformoterol/formoterol and budesonide combination. Clifton et al.[46] found that neonatal birth weight percentile and length were significantly reduced in women using fluticasone/salmeterol (n = 9) compared to budesonide (n = 14). The authors speculated that this may be due to the effects of salmeterol, as fluticasone alone was not associated with these effects. However, this study had a very small sample size and indicated that asthma alone had the greatest negative effect on neonatal outcome. Perrio et al.[47] conducted a postmarketing surveillance study and listed the adverse outcomes without relating them to a control group or to the general population. Neither study provided enough evidence to discourage use of combination asthma preventive therapies.

Long-Acting β_2 Agonists

Overall, the use of LABAs during pregnancy was not associated with any particular adverse event (Table 3). Maternal plasma concentrations after absorption of inhaled salmeterol or formoterol/eformoterol are very low or undetectable.[57] With such low plasma concentrations, it is debatable whether adverse events could be attributed to LABA use.

Mann et al.[49] reported an incident of Aarskog syndrome in an infant whose mother had used salmeterol in the first 4 months of pregnancy. Aarskog syndrome, also known as faciodigitogenital syndrome, is an X-linked syndrome characterized by ocular hypertelorism, anteverted nostrils, broad upper lip, peculiar scrotal "shawl" above the penis, and small hands.[58] However, several of the infant's family members also had this syndrome and the infant had concomitant exposure to ICS and oral corticosteroid, making it impossible to assign this event to any particular drug or to genetics.[49] Jones et al.[51] also reported malformations (bicuspid aorta with penoscrotal fusion, bilateral and unilateral inguinal hernia) in the exposed group; however, the rates of malformations in the exposed (n = 126), unexposed (n = 91), and nonasthmatic (n = 115) groups were 4.7%, 3.9%, and 1.9%, respectively, and were in the range expected in the general population. Seventy-five percent of women were using ICSs concomitantly, but controlling for ICS use did not change the results.

Many studies did not analyze LABAs specifically or control for concomitant use of other asthma medicines. As the use of LABAs during pregnancy with other medications has not shown any increase in harm to the mother or infant, their use alone would be unlikely to pose any risk. While there is currently no established risk with LABA use during pregnancy, more reliable evidence is needed.

Table 2. Studies on the Safety of Combination Asthma Prophylaxis Drugs

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Fluticasone proprionate + salmeterol (pregnancy category C)[19]				
Clifton (2006)[46]	Cohort	Exposed: pregnant asthmatic women using 1. budesonide (n = 14) 2. fluticasone (n = 18) 3. fluticasone + salmeterol (n = 9) Control: pregnant nonasthmatic women (n = 20)	D: fluticasone 783.3 µg/day,[a] salmeterol 108.3 µg/day (third trimester) DF: inhaled	No significant differences in gestational age (39.9 vs 40.2 wk), MBW (3283.0 vs 3423.3 g), mean birth length (50.2 vs 51.8 cm), head circumference (34.9 vs 34.2 cm) with fluticasone + salmeterol vs control Significant differences in birth weight (34.8 vs 74) and length (51.0 vs 88.9) percentile with fluticasone + salmeterol vs group 1
Perrio (2007)[47]	Cohort	Exposed: pregnant asthmatic women (N = 41)	D = fluticasone 50-250 µg + salmeterol 25 µg DF: inhaled	Spontaneous abortion (n = 4), missed abortion (n = 1) Perinatal outcomes: nonketotic hyperglycemia (n = 1), systolic murmurs and small ventricular septal defect (n = 1), apnea episodes thought to be secondary to liquor aspiration (n = 1), undescended right testis (n = 1)

D = dosage; DF = dosage form; MBW = mean birth weight.
[a]Average daily dose was expressed in budesonide equivalent.

Table 3. Studies on the Safety of LABAs

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Eformoterol, Formoterol (pregnancy category C)[19]				
Wilton (2002)[48]	Cohort	Pregnant asthmatic women (N = 33)	D: NR DF: inhaled	Prematurity (n = 5), congenital abnormalities (1 infant with fetal heart rate anomaly, 1 infant with pyloric stenosis)
Salmeterol (pregnancy category C)[19]				
Mann (1995)[49]	Cohort	Pregnant asthmatic women (N = 65)	D = 100 µg/day on average DF: inhaled	Aarskog (faciodigitogenital) syndrome (n = 1); asthma during infancy (n = 2)
Wilton (1998)[50]	Cohort	Pregnant asthmatic women (N = 91)	D: NR DF: inhaled	With first trimester use, ectopic pregnancy (n = 2), spontaneous abortion (n = 7), induced abortion (n = 4), congenital malformation for full-term births (n = 1) (Aarskog syndrome) Congenital anomalies for premature infants (n = 3)
Jones (2002)[51]	Cohort	Exposed: pregnant asthmatic women (n = 126) Unexposed: pregnant asthmatic women using SABAs (n = 91) Unexposed: pregnant nonasthmatic women (n = 115)	D: NR DF: inhaled	Similar rates of malformations (4.7%, 3.9%, 1.9%, respectively); all within the range expected in the general population Malformations in exposed group: bicuspid aorta with penoscrotal fusion (n = 1), bilateral inguinal hernia (n = 1), unilateral inguinal hernia (n = 3) No significant differences among groups in MBW, length, or head circumference of full-term infants or SGA infants
LABAs (nonspecific)				
Bracken (2003)[37]	Cohort	Exposed: pregnant asthmatic women (n = 64) Unexposed: pregnant nonasthmatic women (n = 2153)	D: NR DF: inhaled	No increased risk of IUGR (exposed: 8.3% of 48; unexposed: 7.6% of 2153) No increased risk of preterm delivery (exposed: 10.9% of 64; unexposed: 6.8% of 2141)
Schatz (2004)[39]	Cohort	Exposed (eg, salmeterol, albuterol): pregnant asthmatic women (n = 1828) Unexposed: pregnant asthmatic women (n = 295)	D: NR DF: inhaled	Gestational hypertension (11.8%), preterm delivery (15.8%), low birth weight (13.5%), SGA (7.1%), major malformations (2%, underpowered) No significant relationship between adverse perinatal outcomes and β_2 agonist use
Tata (2008)[45]	Case control	Children with ≥1 major malformation (n = 5124); 25 mothers exposed to LABAs Children with no malformations, matched by year of birth, general practice, singleton or twin (n = 30,053); 131 mothers exposed to LABAs	D: NR DF: inhaled	No increased risk of congenital malformations (<0.5% in both groups)

D = dosage; DF = dosage form; IUGR = intrauterine growth restriction; LABAs = long-acting β_2 agonists; MBW = mean birth weight; NR = not reported; SABAs = short-acting β_2 agonists; SGA =small for gestational age.

Leukotriene Receptor Antagonists

In recent years, several LTRA safety studies[53-55] have been published (Table 4), although doses were often not specified. LTRAs are generally taken in combination with other asthma medications; hence, it is not surprising that not many studies have analyzed this drug class exclusively. Bakhireva et al.[55] stated that 99% of subjects in their LTRA group (n = 96) used SABAs, 40% used oral corticosteroids (majority as burst therapy), and 39% used ICSs at some time during pregnancy. Although 5 major structural defects (Sturge-Weber syndrome, congenital hip dislocation, bilateral club foot, neurofibromatosis type 1, and imperforate anus) were reported in the LTRA group, all 5 mothers also had exposure to ICSs and SABAs, and 2 mothers also had exposure to oral corticosteroids at some time during pregnancy (duration not reported). The prevalence of major structural anomalies at birth in the LTRA group (n = 96) was 5.95% compared with 3.9% among exclusive SABA users (n = 122) and 0.3% among controls (those without asthma; n = 346). Only malformations from the LTRA group were reported, and these major structural defects may have been due to exposure to other medications such as ICSs. In all cases, the mother had used LTRAs throughout pregnancy. Sarkar et al.[53] found a significant decrease in birth weight in the LTRA group, but a subanalysis of women who continued LTRAs throughout pregnancy showed no significant differences in birth weights. Given that 52.6% of participants discontinued LTRAs after the first trimester, the authors suggested that continual LTRA use during pregnancy gave better control of asthma and decreased the risk of low-birth-weight babies.

In the study by Tata et al.[45] (Table 5), LTRAs were combined with cromolyns in a category called "antiinflammatory agents" when reporting adverse events. Among the 36 antiinflammatory agent users, only 1 was exposed to montelukast (control group).

Safety data on LTRAs are limited because large, well-designed studies are lacking.

Cromolyns

Few studies are available on the safety of cromolyns during pregnancy (Table 5). Only the study by Schatz et al.[29] had a reasonably large sample size (n = 243), but the drugs used included inhaled (n = 158), intranasal (n = 113), and ophthalmic (n = 23) forms of cromolyns. As with other studies of preventive asthma drugs during pregnancy, patients were allowed to use oral corticosteroids during periods of exacerbation in all the cromolyn studies. Tata et al.[45] identified 9 cases of congenital malformations with cromolyn use, including congenital hip dislocations and shortening of the legs, imperfect fusion of the skull, defect of the lacrimal passages, cleft palate with bilateral cleft lip, hypospadias, and Down syndrome with ventricular septal defect. However, this study used children born to mothers without asthma as controls and was significantly underpowered, making it difficult to distinguish whether these adverse events could have been due to asthma versus the drugs.

More evidence is needed to link cromolyn use with adverse events given that systemic absorption after inhaled cromolyn delivery is low even after continual dosing.[57]

Discussion

This review has identified few reports of negative outcomes; however, there was no clear, direct association with medication use in most of these cases. Many of the adverse events could have been the result of poorly controlled asthma, rather than medications. A few studies noted poorly controlled asthma as a confounding factor.[8,39,43,44,55] Many studies prospectively followed women who continued their existing asthma treatment and did not control for multiple agents. Other medications not used for asthma were also not controlled for. More safety data are available for older ICSs (eg, beclomethasone and budesonide) and cromolyns, compared to newer medications such as LABAs and LTRAs. Further evidence from large, well-designed studies is essential to confirm the safety of LTRAs and LABAs in pregnant women.

ICSs are the most commonly used preventive asthma medications and are the recommended first-line therapy in moderate to severe persistent asthma during pregnancy by most global organizations (BTS, GINA, NAC, and NHLBI)[3-7]; ACOG and ACAAI[2] recommend cromolyns. Treatment of asthma with ICSs during pregnancy decreased asthma-related physician visits compared to prepregnancy and was not associated with adverse outcomes.[59] The only large study of cromolyns did not show any relationship between major malformations and use of cromolyns in the first trimester.[29] Comparative safety studies of cromolyns and ICSs are lacking, making it difficult to recommend one over the other during pregnancy.

To our knowledge, no data on the budesonide and eformoterol/formoterol combination are available. With low incidences of adverse events from using these agents separately, ICS/LABA combinations would not be expected to cause significant harm. Nevertheless, more safety information on ICS/LABA combinations is warranted.

Evidence for the safety of LTRAs is limited; therefore, some guidelines recommend these agents during pregnancy in cases of inadequate control with first-line antiinflammatory agents and/or if previous or current use of LTRAs has demonstrated efficacy.[2,6,7]

Limitations of Studies Included in the Review

Patient adherence to study medication(s) was taken for granted in most studies, although adherence to asthma

Table 4. Studies on the Safety of LTRAs

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Montelukast (pregnancy category B)[19]				
Merck Registries (2006)[52,a]	Cohort	Pregnant asthmatic women (N = 203)	D: NR DF: inhaled	8 Major congenital anomalies: absent left hand allegedly secondary to amniotic bands (n = 1), hypospadias (n = 2), chordee (n = 1), calcaneal valgus (n = 1), triploidy 69XXY that resulted in termination at 12 gestational wk (n = 1), polydactyly (n = 1), cystic kidney disease (n = 1), bilateral hydroceles (n = 1), cleft tongue (n = 1) No increased risk of spontaneous abortions, low-birth weight, or preterm delivery relative to expected number in general population
Sarkar (2009)[53]	Cohort	1. Exposed: pregnant asthmatic women (n = 180) 2. Unexposed: pregnant asthmatic women using ICSs and inhaled β_2 agonists) (n = 180) 3. Unexposed: pregnant nonasthmatic women exposed to nonteratogens and other innocuous substances (eg, hair dye) (n = 180)	D: NR DF: oral	Outcomes for groups 1 and 2 similar; significant differences between groups 1 and 3 for MBW (3214.1 ± 685.8 g vs 3355.9 ± 657.5 g vs 3424.7 ± 551.1 g), gestational age (37.8 ± 3.1 wk vs 37.6 ± 4.4 wk vs 39.3 ± 2.4 wk), infants with fetal distress (n = 41 vs 22 vs 14) No significant differences in rate of live births, miscarriages, fetal deaths, elective abortions Major malformation in group 1: 1 twin with patent ductus arteriosus, atrial septal defect, congestive heart failure
Zafirlukast (pregnancy category B)[19]				
Twaites (2007)[54]	Cohort	Pregnant asthmatic women (N = 28)	D: NR DF: inhaled	Live births without abnormalities (n = 9), spontaneous abortion (n = 4), therapeutic termination (n = 1)
Leukotriene receptor antagonists (nonspecific)				
Bracken (2003)[37]	Cohort	Exposed: pregnant asthmatic women (n = 9) Unexposed: pregnant nonasthmatic women (n = 2196)	D = montelukast 10 mg daily; zafirlukast 20 mg twice daily DF: inhaled/oral	No increased risk of IUGR (exposed: 16.7% of 6; unexposed: 7.6% of 2195). No increased risk of preterm delivery (exposed: 22.2% of 9; unexposed: 6.8% of 2196)
Bakhireva (2007)[55]	Cohort	1. Exposed: pregnant asthmatic women (n = 96) 2. Unexposed: pregnant asthmatic women who used only SABAs throughout pregnancy (n = 122) 3. Unexposed: pregnant nonasthmatic women (n = 346)	D: NR DF: inhaled/oral	Lower adjusted MBW full-term infants in group 1 (3384 ± 72 g) vs group 2 (3533 ± 68 g) vs group 3 (3529 ± 54 g) 5 Major structural defects reported in group 1: Sturge-Weber sequence (zafirlukast; n = 1), congenital hip dislocation (zafirlukast; n = 1), bilateral club foot (montelukast; n = 1), neurofibromatosis type 1 (montelukast; n = 1), imperforate anus (montelukast; n = 1)

D = dosage; DF = dosage form; ICS = inhaled corticosteroids; IUGR = intrauterine growth restriction; LTRAs = leukotriene receptor antagonists; MBW = mean birth weight; NR = not reported; SABAs = short-acting β_2 agonists.

[a]Secondary evidence from Bakhireva et al.[55]

Table 5. Studies on the Safety of Cromolyns

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Nedocromil (pregnancy category B)[19]				
Wilton (1998)[50]	Cohort	Pregnant asthmatic women (N = 81)	D: NR DF: inhaled	With first-trimester exposure, spontaneous abortion (n = 1), elective abortion (n = 8), congenital heart disease anomaly (n = 1)
Schatz (2004)[39]	Cohort	Exposed: pregnant asthmatic women (n = 60) Unexposed: pregnant asthmatic women (n = 2063)	D: NR DF: inhaled	Preeclampsia (13.3%), preterm delivery (21.7%), low birth weight (20%), SGA (16.7%, underpowered), major malformations (3.3%, underpowered) No significant relationship between adverse perinatal outcomes and cromolyn use
General cromolyns (nonspecific)				
Schatz (1997)[29]	Cohort	Exposed: pregnant asthmatic women (n = 243) Unexposed: pregnant nonasthmatic women (n = 1247)	D: NR DF: various	No significant relationships between major congenital malformations and first-trimester use (exposed: 6.0% of 151; unexposed: 5.0% of 1348) or anytime use (exposed: 6.2% of 243; unexposed: 4.9% of 1247)
Bracken (2003)[37]	Cohort	Exposed: pregnant asthmatic women (n = 22) Unexposed: pregnant nonasthmatic women (n = 2183)	D: NR DF: various	No increased risk of IUGR (exposed: 0% of 18; unexposed: 7.7% of 2183) Increased risk of preterm delivery (exposed: 18.2% of 22; unexposed: 6.8% of 2183)
Tata (2008)[45]	Case control	Children with ≥1 major malformation (n = 5124); 9 mothers exposed to cromolyns or LTRAs Children with no malformations, matched by year of birth, general practice, and singleton or twin (n = 30,053); 27 mothers exposed to cromolyns or LTRAs	D: NR DF: inhaled	No increased risk of system-specific malformations, apart from a large relative increase in musculoskeletal system malformations in children with prenatal exposure to cromolyns Congenital hip dislocation (n = 3), congenital shortening of leg (n = 1), imperfect fusion of skull (n = 1), defect of lacrimal passages (n = 1), cleft palate with bilateral cleft lip (n = 1), Down syndrome with ventricular septal defect (n = 1), hypospadias (n = 1)

D = dosage; DF = dosage form; IUGR = intrauterine growth restriction; LTRAs = leukotriene receptor antagonists; NR = not reported; SGA = small for gestational age.

medications has been shown to decrease in pregnancy.[18] Sarkar et al.[53] found that 52.6% of their subjects discontinued montelukast after the first trimester. Adherence was measured only in a few studies. Dombrowski et al.[30] used self-reports, serum theophylline concentrations, pill counts, and beclomethasone canister weights to measure adherence, while Bakhireva et al.[40] conducted phone interviews to inquire about actual use, frequency, and dosage in accordance with medical records. Several studies reviewed here used prescription records as a means to follow a subject's medication use.[35,47,48-50,54] Prescription event monitoring (PEM) studies are also heavily reliant on prescribers' documentation, as outcomes are measured using questionnaires that are filled in by treating physicians, which may not always be reliable. Health-care providers may have also been underprescribing, especially when confronted with an asthmatic pregnant patient. Not adhering to asthma management guidelines could also be the cause of poor asthma control, which could be linked to some of the adverse events documented.

Asthma severity may worsen during pregnancy.[1] Most studies included participants with a range of asthma severities; however, few controlled for asthma severity. Dombrowski et al.[30] only included participants with moderate asthma and excluded those with unstable or severe asthma; Greenberger and Patterson[26] targeted pregnant women with severe asthma; Wendel et al.[28] targeted severe asthmatic pregnant women who had been hospitalized; and Stenius-Aarniala et al.[17] included only pregnant women with acute asthma. Women with uncontrolled or severe asthma can also be considered as having a high-risk pregnancy, which could have been the reason for a high incidence of cesarean births.[60] Other confounding factors, such as smoking, illicit drug use, diet, ethnicity, comorbidities and other medications, including nonprescription medications, may have contributed to the negative outcomes reported in many studies. Understandably, nearly all studies permitted subjects to use oral corticosteroids and SABAs when needed for exacerbations. It is impossible to attribute an adverse event to a particular drug when participants are using multiple medications.

Reporting of participant characteristics and outcomes also varied among studies. Some studies listed all the adverse events, but did not clearly state whether more than one of those events was associated with the same pregnancy.[39,46,48,49,55] Kallen et al.[31] listed malformations categorically without an indication of whether multiple malformations occurred in the same infant. The relationship between gestational exposure time and adverse event was not explored in depth; however, a few studies identified most of the adverse events occurring due to exposure in the first trimester.[49,50] Dosage ranges were also poorly documented in the majority of studies, and more than 1 dosage form

was sometimes included.[29,34,37,39,45,55] Furthermore, sample sizes in many studies were small. Missing data and loss to follow-up were also evident in many studies, further skewing the results.

Strengths and Limitations of the Review

This is an up-to-date review of the safety of preventive asthma medications during pregnancy. The review team comprised respiratory and neonatal physicians and pharmacists. A thorough and comprehensive search was conducted to ensure that all relevant articles were identified. To minimize the chances of missing studies, reference lists of already published reviews were also reviewed. However, data from the Merck report[52] were extracted from a secondary source because the original documentation was not available. Two authors reviewed each article and verified the data extracted to reduce the potential for bias in the interpretation of data.

The majority of studies were carried out in North America and Europe; asthma medication safety studies during pregnancy from other parts of the world were limited, which makes the review less generalizable to patients from other regions, especially ethnic minorities.

Message for Practitioners

Until further evidence from large, well-designed studies in pregnant women is available, health-care providers should follow asthma guidelines produced by various professional organizations for the management of asthma during pregnancy (ACOG and ACAAI, BTS, GINA, NAC, and NHLBI).[2-7] A conservative approach would be to use the lowest effective dose of medications with more safety data, such as ICSs and cromolyns. However, health-care providers should not hesitate to increase doses or introduce additional medications as needed, but only after verifying patient adherence and inhaler techniques. The negative outcomes reported in some studies should not discourage prescribers from making appropriate dosage increases of ICSs or introducing other agents, such as LABAs, during pregnancy. A collaborative approach involving an obstetrician, a respiratory specialist, and other health-care providers should be considered in complicated cases.

Summary

Some negative outcomes of preventive asthma medicines have been reported, although there is no clear, direct association with medication use in most of these cases. More safety data are available for older ICSs and cromolyns compared to newer medications such as LABAs and LTRAs. Selection of preventive drugs for asthma management during pregnancy should be based on an assessment of the risks and benefits of medication use versus the risks of poorly controlled asthma for the mother and the unborn child.

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Una Revisión Sistemática de la Seguridad del uso de Medicamentos Preventivos Para el Asma Durante el Embarazo

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EXTRACTO

OBJETIVO: El asma descontrolada durante el embarazo pone en riesgo a la mujer y a su hijo por nacer. Las guías para el manejo de asma (Colegio Americano de Obstetras y Ginecólogos, Asma e Inmunología, Sociedad Torácica Británica, Iniciativa Global para el Asma, Concilio Nacional de Asma de Australia y el Instituto Nacional del Corazón, Pulmón y Sangre) recomiendan que el uso de medicamentos para asma durante el embarazo deba ser optimizado. El objetivo fue revisar la seguridad de medicamentos preventivos para el asma durante el embarazo.

FUENTES DE DATOS: Las siguientes bases de datos fueron buscadas desde su inicio hasta febrero de 2011: Ovid MEDLINE, PubMed, Cochrane library, EMBASE, y CINAHL plus.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: La búsqueda estuvo limitada a estudios en humanos y artículos en inglés. Los títulos de los artículos fueron cernidos por relevancia. Extractos de artículos relevantes fueron revisados para confirmar relevancia antes de obtener el texto completo.

SÍNTESIS DE DATOS: Los artículos seleccionados fueron leídos por 2 autores y la precisión de los datos extraídos fue confirmada.

RESULTADOS: Treinta y tres artículos fueron incluidos en la revisión final; muestras de tamaño pequeño, falta de datos, control no adecuado de factores confusos y pobre documentación del rango de dosis fueron limitaciones comunes de los estudios revisados. El uso de corticosteroides inhalados (ICSs), cromolinos y agonistas β_2 de larga acción (LABAs) durante el embarazo no estuvo asociado con resultados pobres en los estudios de pos mercadeo. Malformaciones congénitas han sido reportadas con el antagonista del receptor de leucotrieno (LTRA) por exposición durante el embarazo, pero esas mujeres estuvieron también expuestas a otros medicamentos incluyendo corticosteroides orales.

CONCLUSIONES: Algunos resultados negativos por el uso de medicamentos preventivos para el asma han sido reportados, aunque su conexión directa con el uso de medicamentos ha sido inconclusa. La selección de medicamentos preventivos para el manejo del asma durante el embarazo debe basarse en una evaluación de los riesgos y beneficios contra los riesgos de un asma pobremente controlada.

Traducido por Homero A Monsanto

Revue Systématique de la Sécurité des Médicaments Antiasthmatiques chez la Femme Enceinte

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RÉSUMÉ

OBJECTIFS: L'asthme mal contrôlé durant la grossesse place la mère et l'enfant à risque. Les lignes directrices pour le traitement de l'asthme (American College of Obstetricians and Gynecologists, American College of Allergy, National Asthma Council of Australia, et la National Heart, Lung and Blood Institute), recommandent d'optimiser l'utilisation des médicaments antiasthmatiques durant la grossesse.

SOURCE DE L'INFORMATION: Les bases de données suivantes ont été scrutées jusqu'en février 2011: Ovid, MEDLINE, PubMed, Cochrane Library, EMBASE, et CINAHL plus.

SÉLECTION DES ÉTUDES ET EXTRACTION DE L'INFORMATION: La recherche a été limitée aux études réalisées chez l'humain et publiées en langue anglaise. Les titres de tous les articles ont servi pour en évaluer la pertinence. Les résumés des articles pertinents ont été révisés pour confirmer la pertinence avant d'obtenir l'article complet.

SYNTHÈSE DE L'INFORMATION: Les articles sélectionnés ont été lus par 2 des auteurs et l'exactitude des informations extraites a été confirmée.

RÉSULTATS: Trente trois études ont été incluses dans la révision finale. Une petite taille d'échantillon, des données manquantes, un contrôle inadéquat des facteurs confondants et une mauvaise documentation des doses constituaient les principales faiblesses des études révisées. L'utilisation de corticostéroïdes inhalés (CSI), du cromoglycate, et des agonistes β_2 longue action (ABLA) durant la grossesse n'est pas associée à des effets indésirables durant la grossesse. Cependant, l'association de fluticasone/salmeterol a été associée à des événements indésirables dans les études post-commercialisation. Des malformations congénitales ont été rapportées avec les antagonistes des récepteurs des leukotriènes durant la grossesse, mais ces femmes ont aussi été exposées à d'autres médicaments dont les corticostéroïdes.

CONCLUSIONS: Quelques événements indésirables ont été rapportés avec les médicaments antiasthmatiques, bien que le lien d'imputabilité ne soit pas concluant. Le choix des médicaments antiasthmatiques durant la grossesse devrait être basé sur une évaluation des bénéfices et des risques associés aux médicaments par rapport à ceux de l'asthme mal maitrisé.

Traduit par Marc Parent