



Asthma, asthma medications and their effects on maternal/fetal outcomes during pregnancy

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ABSTRACT

Maternal asthma may increase the risk of adverse fetal and maternal outcomes such as low birth weight, perinatal mortality, preterm birth, preeclampsia, hypertensive disorders, maternal mortality, uterine hemorrhage, and gestational diabetes. Controlling asthma during pregnancy with appropriate medications leads to improved intrauterine growth of the fetus and fewer adverse perinatal outcomes. Prospective population or birth cohort studies have shown that the medications used to treat asthma, such as bronchodilators (short-acting β_2 -agonists) and controller medications (inhaled corticosteroids, cromones, theophylline, leukotriene inhibitors), have no or minimal effects on fetal growth, and perinatal complications are reduced when maternal asthma is adequately controlled. However, taking oral corticosteroids during pregnancy may confer increased risk of lower birth weight and congenital malformations. Therefore, managing pregnant asthmatics requires a careful benefit–risk analysis, and when indicated, the benefits of a medication that may have increased risks can dictate its use in severe uncontrolled asthma.

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1. Introduction

Asthma is a chronic inflammatory disease of the lower airways that produces bronchial obstruction that is variable, resulting in symptoms of wheezing, shortness of breath, chest tightness, and cough, and often responds to treatment. The inflammation is driven in many cases by a subset of T lymphocytes (Type 2 helper T cells [Th-2 cells]) that elaborate certain specific cytokines, such as interleukin (IL)-4, IL-5, and IL-13, that recruit, sustain, and perpetuate the chronic infiltration of inflammatory cells (e.g., eosinophils, neutrophils) that populate the airways [1]. Management of the disease therefore must include medications that are anti-inflammatory (referred to as controller medications), as well as medications to relieve the acute symptoms (referred to as reliever medications). Since the medications used to treat this disease can cause unwanted side effects, which can harm the mother, as well as the fetus, there must be a careful analysis of the benefits and risks before using them [2].

Asthma is one of the most common chronic medical conditions to complicate pregnancy and the most common respiratory disorder to do so. The prevalence of asthma is increasing world-wide in general and in the USA in particular. Approximately 4–8% of pregnant women carry a diagnosis of asthma [3]. Evidence suggests

that there is a two-fold effect of asthma: it can impact adversely the outcome of the pregnancy, and conversely, the pregnancy may alter the clinical status of a woman with the disease. Having insight into the mechanisms of these events may positively influence one or both of the outcomes. The interaction between asthma and asthma management on pregnancy is reviewed here with regard to the clinical outcomes and where known, the underlying mechanisms.

2. The effect of maternal asthma on pregnancy outcomes

Asthmatic women have an increased risk of complications during pregnancy as a result of inadequately controlled asthma and/or some of the asthma medications used to manage these patients. Poorly controlled asthma can lead to a feeling of being air hungry due to reduced levels of maternal oxygen in the lung and blood, low levels of carbon dioxide in the blood due to hyperventilation, and an inadequate supply of oxygen to the fetus [4]. Other risk factors that contribute to poor pregnancy outcomes include lung inflammation, smoking, obesity and altered placental function. In the mother, these effects can translate into preterm labor, placenta previa, cesarean section, prolonged hospital stay, and hypertensive disorders including preeclampsia [4–6]. Severe acute maternal asthma is associated with maternal mortality, fetal mortality, or both [6]. Therefore, prevention of acute or severely uncontrolled asthma in female patients may reduce the likelihood of such an outcome when pregnancy occurs.

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Table 1
Relationship of asthma control and incidence of preterm delivery.

Measures of asthma control and exacerbation	Incidence of preterm delivery	
Asthma control in first part of pregnancy	Adequate – 6.3% Inadequate – 11.4%	$P=0.02$
Hospitalization for asthma Exacerbation during pregnancy	Yes – 16.4% No – 7.6%	$P=0.02$

Adapted from Bakhirara et al. [9].

2.1. Preterm delivery

As mentioned above, the severity of asthma increases the risk of preterm delivery. In one study, women hospitalized for their asthma (Table 1) had a significantly ($P=0.02$) higher incidence (16.4%) of preterm delivery (<37 weeks gestation) versus asthmatic women without hospitalization (7.6%) during their pregnancy [9]. In another report, preterm delivery was associated with severe asthma which was also shown to correlate with the rate of cesarean deliveries, where increases were found in moderate to severe asthmatics compared to controls [10].

2.2. Low birth weight

The level of maternal lung function as measured by forced expiratory volume in the first second (FEV1), which can reflect the severity of the disease and degree of airway remodeling, correlates with the risk of an infant being born with low birth weight or a Ponderal index <2.2 [8]. That is, pregnant mothers with an FEV1 in the lowest tertile (<83% predicted) were significantly more likely to have an infant whose birth weight was in the lowest quartile (<2150 g). Reduced birth weight (<2500 g) occurs 2.5-times more frequently in asthmatic women who have had an asthma exacerbation during pregnancy, in contrast to women who did not have an exacerbation during their pregnancy [7]. A low Ponderal index as well as low birth weight indicates that asymmetric intrauterine growth retardation (IUGR) has occurred. Abnormalities in birth weight can present as: preterm and appropriately grown, preterm and growth retarded, or full term and growth retarded. Symmetrical growth retardation refers to whether all morphometric measurements are reduced, while asymmetrical retardation refers to reduced birth weight with normal length and head circumference [7].

In a large prospective study that investigated the effect of asthma on the rates of adverse pregnancy and fetal outcomes, black and white women 15–44 years of age enrolled in the Tennessee Medicaid Program were followed during pregnancy from 1995 to 2003 [11]. Claims data were used to determine the effects of asthma exacerbations on pregnancy and infant outcomes. Of the over 140,000 pregnancies, 6.5% occurred in women with asthma. Twenty-three per cent of the women with asthma received care in a hospital or emergency room during their pregnancy with a larger proportion of black women being treated than white women (40% versus 23%). Birth weights of infants from mothers with asthma were on average 38 g less, while infants from women who had asthma exacerbations during pregnancy were 56 g less than infants from women without asthma, after controlling for race and other covariates. Other adverse outcomes included a higher percentage of asthmatic women with hypertensive disorders of pregnancy, membrane-related disorders, preterm labor, ante-partum hemorrhage, and cesarean delivery. Thus, asthma is a risk factor for several adverse outcomes of pregnancy and poorly controlled asthma during pregnancy substantially increases these risks.

2.3. Congenital malformations

There is a lack of consensus in the literature regarding the effect of maternal asthma by itself on the development of congenital malformations. However, a recent population-based cohort study involving over 41,000 pregnancies in women in Canada between 1990 and 2002 provided data to suggest that maternal asthma increases the risk of specific groups of congenital malformations [12]. The crude prevalences of any malformation were 9.5% for women with asthma and 7.5% in women without asthma. In addition, there was a significant association (OR 1.30; 95% CI 1.20–1.40) for maternal asthma and any malformation in three specific groups: nervous system (excluding spina bifida) OR 1.83; 95% CI 1.37–2.83; respiratory system OR 1.75; 95% CI 1.21–2.53; and digestive system OR 1.48; 95% CI 1.19–1.85. Thus maternal asthma itself increases the risk of specific groups of congenital malformations.

The same group also examined whether severe loss of asthma control, resulting in an exacerbation that occurred during the first trimester of pregnancy was linked to an increased risk of congenital malformations [13]. A cohort of 4344 pregnancies in asthmatic women was assessed during 1990 and 2000. Asthma exacerbation was defined as a filled prescription for oral steroids, an emergency department visit, or hospitalization for asthma. The presence of a malformation was documented by the diagnosis obtained from the data bases. From the cohort, 398 (9.2%) infants were identified with at least one malformation and 261 (6.0%) with a major malformation. The adjusted odds ratio for these malformations was 1.48 (95% CI 1.04–2.09) and 1.32 (95% CI 0.86–2.04), respectively, as compared to women who did not have an exacerbation during the first trimester. These data suggest that in addition to the disease itself, loss of asthma control in early pregnancy further increases the risk of congenital malformations. However, the authors could not claim that the association they found was causal because of a residual confounding that might be present due to the use of oral corticosteroids in some of the patients.

Based on a recent review of 502 cases of cardiac anomalies in the New York State Congenital Malformations Registry and 1066 controls, Lin et al. [14] have suggested that maternal asthma status (controlled versus uncontrolled, mild versus severe) and asthma medication use started in the peri-conceptual period, particularly bronchodilators, may be associated with an increased risk of fetal cardiac defect. Although this case-control study had limitations of sample size, lack of information on medication dosage, frequency of usage, and timing of exposure, it points to the need for further study of the maternal asthma severity and maternal medication use in association with congenital defects.

It has been hypothesized that the airway inflammation, by causing maternal hypoxia, can result in fetal oxygen impairment. Indeed, there is evidence that oxygen levels in the fetus are tightly controlled in the first trimester of pregnancy and hypoxia at this crucial time in development can cause abnormal fetal changes resulting in some of these malformations [15]. However, further studies are needed to separate the confounding effect of medication use during pregnancy and these malformations.

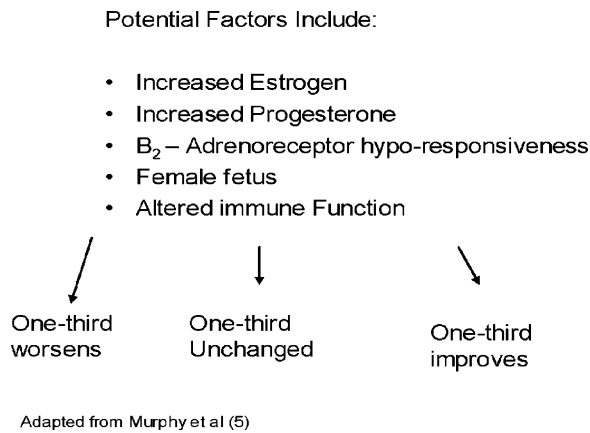


Fig. 1. Effect of pregnancy on maternal asthma.

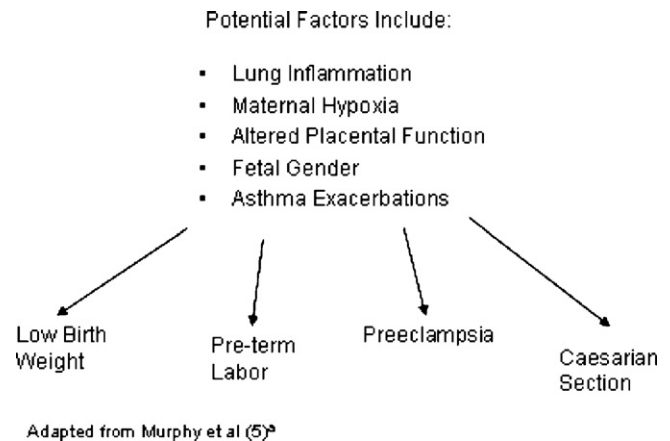


Fig. 2. Effects of maternal asthma on pregnancy and perinatal outcomes^a.

3. Effect of pregnancy on asthma

3.1. Variability of effect

It has been reported over the years that pregnancy itself can have a varying effect on a female's asthma including making it worse, making it better, or having no effect on the status during pregnancy. Some of the factors proposed for these effects are depicted in Fig. 1 in some individuals, cases of severe life-threatening asthma have occurred requiring termination of the pregnancy during the first trimester [16]. The asthma in these subjects improved within 24 h after termination of the pregnancy. Asthma symptoms may worsen or improve at various points during pregnancy. For example, clinical changes, good or bad occurred frequently during the 2nd trimester (25–32 weeks gestation) of pregnancy, while wheezing and interference with sleep tended to improve in the last few weeks of pregnancy (37–40 weeks gestation) in all subjects [9]. The majority of subjects follow the same course with their asthma in a subsequent pregnancy.

Emergency room visits and hospitalizations for asthma occur during pregnancy at low rates for mild disease but the frequency increases as the severity of asthma worsens [17]. In this study of over 1700 pregnant asthmatics, exacerbations of asthma occurred in the majority of all severe asthmatics, while in patients with mild asthma exacerbations, they occurred in only 12% of patients during pregnancy. Severe asthma was associated with the occurrence of hospitalizations, symptoms, increased steroid requirements and unscheduled office visits to the doctor in approximately 20% of subjects during pregnancy. Of note, asthma symptoms per se do not worsen during labor or delivery, but if they do, they are usually managed with bronchodilators with good success.

Not only can the disease process alter pregnancy outcome in the mother and fetus, but fetal gender can influence these events as well. In a prospective study, 702 pregnant women with a diagnosis of asthma were recruited from over 70 practices in southern New England between 1997 and 2000 [18]. Using a measure of lung function to determine airway lability, peak expiratory flow (PEF) was measured twice daily and the difference between morning and afternoon values (termed peak flow lability) was calculated at various time-points during pregnancy. PEF lability was greater (9.9%) in women carrying female fetuses than those carrying male fetuses. This difference was detected throughout pregnancy and seems to indicate that pregnant asthmatic women carrying a female fetus are at greater risk of worsening maternal asthma than those women carrying a male fetus.

Placental physiology, including placental blood flow, which supplies nutrients to the fetus, and an enzyme referred to as 11 β -

hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which protects the fetus from excess maternal glucocorticoids, has been demonstrated to affect fetal growth during pregnancy. Placenta obtained from women with moderate to severe asthma exhibited reduced dilator and constrictor vascular responses compared to placenta from women with mild asthma or non-asthmatic controls [19]. This may indicate that altered placental blood flow in asthmatics with more severe disease may contribute in part to reduced fetal growth by providing fewer nutrients to the fetus. In addition, the placenta of pregnant asthmatics carrying female fetuses had significantly less 11 β -HSD2 enzyme activity which correlated with the decreased growth of their female baby at birth [20].

3.2. Proposed mechanisms of action

It has been proposed that altered β 2-adrenoreceptor responsiveness, increases in maternal circulating hormones, and/or fetal gender may be involved in the mechanisms that underlie the physiologic alterations that are seen with asthma during pregnancy [5]. Certain endogenous hormones are elevated during pregnancy that may be beneficial to the patient with asthma such as serum-free cortisol, which has anti-inflammatory properties, and progesterone, which increases normal minute ventilation during normal pregnancy and is also a smooth muscle relaxant (Fig. 2). Progesterone can also have negative effects and may worsen asthma by reducing β 2-adrenoreceptor responsiveness and potentiating inflammation [4]. Differing levels of certain circulating hormones in an individual patient during pregnancy may account in part for why some patients' asthma worsens while other patients' asthma is improved. In addition to hormones, which can be immunomodulatory, increased inflammatory cytokines produced in the airway and increased smooth muscle reactivity (a key feature in asthmatics) might have a common pathophysiologic pathway [21].

4. Poor asthma control during pregnancy influences maternal and perinatal outcomes

Just as asthma the disease may increase the risk in pregnant women of perinatal mortality, preeclampsia, low birth weight and/or preterm birth, a generally accepted hypothesis is that uncontrolled asthma increases perinatal risks while well controlled asthma reduces these risks (reviewed in reference [17]). Since severe asthma is associated with maternal and fetal mortality, the assumption made is that preventing asthma from becoming acutely or severely uncontrolled would likely prevent or decrease this mortality. It has also been pointed out [22] that when asthma

is prospectively managed during pregnancy by a specialist, fewer adverse fetal or maternal outcomes occur.

There is a trend in certain populations of pregnant women to under-medicate themselves or stop their medications altogether. This unfortunate circumstance was demonstrated in a prospective study of a large cohort of over 112,000 pregnant women enrolled in the Tennessee Medicaid program who delivered single births during the interval between 1995 and 2001 [23]. Medication use was determined from weekly prescription claims data. Women with asthma decreased their asthma medication use significantly during 5–13 weeks of pregnancy. The number of prescriptions for inhaled steroids was reduced by 23%, short-acting β_2 -agonist reduced by 13%, and oral steroids by 54%. It was not clear from the data why the women discontinued their medication in the first trimester, but the behavior could reflect either a fear that the medication might have caused adverse effects in their fetus or a belief that their asthma had improved during the pregnancy.

Poor asthma control led to increased risk of preterm delivery or impaired fetal growth in a cohort of 719 asthmatic women followed between 1998 and 2003 by the Organization of Teratology Information Specialists (OTIS) Asthma Medications in Pregnancy Study [9]. The incidence of preterm delivery, IUGR, and mean birth weight were evaluated with relationship to asthma symptom control and exacerbation measures. Preterm delivery was significantly ($P=0.02$) higher in patients with inadequate asthma symptom control in the first trimester (11.4%) compared with patients with adequate asthma control (6.3%). Furthermore, patients who exacerbated during pregnancy had a significantly ($P=0.02$) increased rate (16.4%) of preterm delivery versus 7.6% for patients who did not experience an exacerbation during their pregnancy. These frequencies of adverse pregnancy outcomes were independent of corticosteroid use or other confounders.

Poorly controlled asthma, possibly leading to fetal hypoxia, has been thought to be a potential mechanism to explain the association between asthma and IUGR [5]. Furthermore, factors that determine gestational length and preterm birth may be more sensitive to uncontrolled asthma than factors that influence fetal growth. Hypoxia is a major factor in the asthmatic woman and its occurrence at the maternal/fetal interface over extended periods of time during pregnancy could lead to low birth weight and preterm babies. These observations suggest that uncontrolled asthma may increase the risk of perinatal mortality by lowering the weight of the baby and increasing the risk of a preterm delivery since birth weight and gestational age at birth are very strong predictors of perinatal mortality.

5. Reproductive issues in the development of asthma medications

The treatment goals for the pregnant asthma patient are to provide optimal therapy to maintain control of asthma for maternal health and quality of life as well as for normal fetal maturation [24]. Asthma control means that the patient should have minimal or no chronic symptoms day or night, minimal or no exacerbations, no limitations on activities, maintenance of near normal lung function, minimal use of short-acting inhaled β_2 -agonists, and minimal or no adverse effects from medications. In order to control the inflammation in the lung, anti-inflammatory medications such as inhaled corticosteroids, leukotriene inhibitors, or chromones are used, while bronchodilators such as β_2 -agonists or theophylline are used to relieve acute symptoms. These medications have been evaluated in both pre-clinical and clinical studies to establish their effects on pregnancy and fetal development. Considered below are some of the issues that are raised during the pharmaceutical development of anti-asthma medications.

5.1. Toxicologic considerations

Antagonism of a target by a pharmaceutical agent during pregnancy may cause adverse reproductive outcomes in the fetus depending on a number of important factors which determine its teratogenic potential in humans including [25]:

- Route of administration
- Metabolism
- Dose
- Whether the agent crosses the placenta at the point of development at the time of exposure
- Pharmacologic activity
- Non-target mediated effects
- Binding affinity to target in relation to inactive or active forms of the receptors
- Toxicokinetics

Those factors related to the target include:

- Maternal and fetal tissue distribution
- When during organogenesis it is expressed
- Whether or not the target is expressed in human tissues versus animals
- Structural similarity of the organs in humans versus animals

Standard embryo-fetal toxicity studies are conducted in rats, rabbits and/or mice by the route of administration for which the agent will be ultimately marketed. All pregnant animals (dams) are observed usually twice daily for morbidity and mortality during the study period, as well as for food consumption and body weight at least once daily for signs of clinical toxicity. At the end of the gestational period the animals are sacrificed so that potential toxic effects of the pharmaceutical agents can be determined on the pregnant animal and the fetus.

Small molecules are usually administered to rats and rabbits systemically over a range of doses to achieve very high levels in the mothers during gestational days (GD) 6–17 in rats and 6–19 in rabbits, corresponding to the sensitive period of organogenesis. Cesarean sections are then carried out toward the end of gestation (GD 20–21 in rats and GD 28–30 in rabbits). If there are no malformations or fetal findings, then placental transfer studies are conducted to demonstrate that the small molecules cross the placenta. Non-human primates are utilized for developmental and reproductive toxicity (DART) studies relating to large molecules like monoclonal antibodies, in the absence of alternative relevant species. In the latter instance, pregnant cynomolgous monkeys are usually treated weekly via systemic route from gestational day 20 to birth (ca day 150). From an exposure standpoint, there are substantial differences between times of placental transfer for small molecules and antibodies with the former usually occurring in early pregnancy while placental transfer of the latter does not occur until later in pregnancy [26]. In addition, information about potential reproductive issues is also gleaned from experiments in mice in which the genes of the target are deleted (knock-out mice) and the resulting effects on maternal fertility and fetal development are observed. Usually these results are predictive of the type of developmental issues that one may anticipate but in some instances the malformations that are seen during DART studies may be different from that seen with gene deletion studies. These differences may come about as a result of a number of factors mentioned above.

5.2. VLA4 antagonism as a specific example of issues related to asthma drug development

VLA4 (integrin $\alpha 4\beta 1$) and its cell surface ligand VCAM-1 play an important role in cell-cell interactions in many species (e.g., mice, rats rabbits) including reproductive functions such as fertilization, embryo implantation, and placental development, as well as cardiac development. By gestational day 10/11 in mice the $\alpha 4$ sub-unit is expressed on the chorion and VCAM-1 is expressed on the allantois and myocardium and is involved in chorioallantoic fusion and formation of the spiral septum [27,28]. Three specific and potent small molecule VLA4 antagonists were developed as a potential treatment for asthma by Aventis Pharmaceuticals [29,30]. There were differential effects on reproduction and development by the three compounds that were identified in the DART studies. IVL 745 did not cause any significant maternal or fetal effects at doses up to 100 or 250 mg/kg/day in rats and rabbits, respectively. HMR1031 treatment resulted in marked maternal toxicity and slight fetal toxicity at the highest tested doses of 75 and 200 mg/kg/day in rabbits and rats, respectively. IVL984 treatment resulted in minimal maternal effects at doses up to 15, 40 and 100 mg/kg/day in rabbits, rats and mice, respectively. In contrast, marked developmental effects were seen at the lowest tested doses of 0.2, 1, and 3 mg/kg/day in rabbits, rats, and mice, respectively. The latter embryo-fetal effects included total post-implantation loss due to early resorptions, and elevated incidences of cardiac and skeletal malformations. Embryonic exposure levels of drug alone did not explain the differences in developmental toxicities. Several potential factors were postulated including differences in:

- Pharmacologic potency of the three compounds
- Clearance rates
- Amount of protein binding
- Species differences in the conformational state of the VLA4 receptor subtypes for VLA4
- Structural characteristics of the molecules

Considerations regarding the predictive value of these findings to humans include:

- Since cardiac development is highly conserved, one would expect these effects in other species.
- There are species differences in the expression of these targets as $\alpha 4$ integrins and VCAM-1 are not expressed on human placental primordium.
- The human placenta is structurally different from rodents or rabbits so it is difficult to predict whether or not these effects would occur on human placentation.
- That small molecule effects for a particular target such as VLA4 may differ from those of large molecules directed against the same target as demonstrated by the fact that an anti-VLA4 antibody has been used successfully in the clinic without reproductive issues.

6. Risk evaluation associated with asthma medication use during pregnancy

6.1. General considerations

The decision to treat a pregnant asthmatic woman with controller (anti-inflammatory) and reliever (bronchodilator) medications involves a discussion of the benefits of each drug and their potential risks of adverse effects. The benefits of the appropriate use of asthma medications are better control of the underlying disease and fewer complications during pregnancy. There is a sec-

ondary gain for the fetus she is carrying since the best environment for growing a healthy baby is a healthy mother. The critical issue is whether the potential adverse effects of a given asthma medication on embryo or fetal development outweigh the substantial potential benefit of improving the mother's asthma. The evaluation of potential risks on pregnancy outcome of administering asthma medication is informed by both human and animal data.

6.2. Human data

There are several challenges to obtaining adequate human data to assess the benefits and risks of asthma medication during pregnancy. The best methodology for evaluating human response to therapy is collecting data in a randomized controlled trial. However, this type of trial is generally not feasible to assess the safety of medication during pregnancy, in part, because it would entail exposing a subset of pregnant women to medication they did not need. In addition, case control and cohort studies may suggest an association of a drug with an adverse maternal or fetal outcome, but they do not by themselves prove causality. In part, this is due to the fact that they are often limited by inadequate sample size (i.e., underpowered to show a statistically significant effect if there was one).

6.3. Animal data

An alternative way to ascertain data to evaluate human drug risks is by performing animal developmental toxicology experiments (reviewed in references [24,6]). Animal studies are designed to maximize the potential toxic effects of the test medication by using large doses. Therefore, a negative result in animal studies for an investigative agent indicates a low potential for human developmental toxicity. Surprisingly, positive animal data is less predictive for human toxicity because one cannot differentiate whether the results are due to species differences, whether clinically irrelevant high doses were used, or whether maternal toxicity was responsible for the adverse effects in the offspring [9,6]. However, it should be noted that there are no clear data available indicating that severe maternal toxicity is responsible for fetal dysmorphogenesis that leads to cardiac malformations. Timing of exposure versus timing of developing organs should also be considered. Human to animal comparison of exposure (C_{max} , AUC) data is a better endpoint to assess this risk, rather than therapeutic dosages. The adverse fetal effects most often mentioned that can be linked to severe maternal toxicity include retarded fetal growth or fetal death.

6.4. Drug label categories and step therapy recommendations

The Food and Drug Administration (FDA) has grouped medications used in pregnancy into risk categories for labeling purposes using a system summarized in Table 2 [31]. Developed as a guide for selection of therapy for use during pregnancy, this system although useful, suffers from some drawbacks including a paucity of "adequate and well controlled" data on drug effects in humans, resulting in an over reliance on animal data. In addition, clinical interpretation of the "C" category is very difficult and does not take into account the route of administration, potential pharmacokinetic and pharmacodynamic changes that occur during pregnancy. To date, no asthma medication is labeled in category A because negative animal reproductive toxicology studies and negative adequate and well controlled human trial data are required and none satisfy these criteria. Of note, only one inhaled glucocorticosteroid (budesonide) is labeled in category B based on good safety results from a population-based Swedish Medical Birth Registry [32]. Table 3 depicts the recommendations for step therapy of chronic persistent asthma during pregnancy. These recommendations derive from a

Table 2
Food and Drug Administration pregnancy categories^a.

Category risk	Animal studies	Human data	Benefit may outweigh
A	Negative ^b	Studies ^c negative	Yes
B	Negative	Studies not done	Yes
B	Positive ^d	Studies negative	Yes
C	Positive	Studies not done	Yes
C	Not done	Studies not done	Yes
D	Positive or negative	Studies or reports positive	Yes
X ^e	Positive	Studies or reports positive	No

^a Reprinted from reference [31] with permission.^b No teratogenicity demonstrated.^c "Adequate and well-controlled" studies in pregnant women.^d Teratogenicity demonstrated.^e Drug is contraindicated in pregnancy.

number of population-based cohort studies that have evaluated drug treatment in asthmatic women during pregnancy and are summarized here:

- Those patients who are adequately controlled on a program of asthma medications when they become pregnant should remain on them including inhaled corticosteroids, theophylline, cromolyn, or long-acting β_2 -agonists. Leukotriene antagonists such as montelukast or zafirlukast could be continued to the extent that they were effective in patients with moderate to severe asthma. Zileuton should be discontinued during pregnancy [24].
- Patients who require oral steroids despite high doses of inhaled steroids and long-acting β_2 -agonists should be maintained on the lowest effective daily dose of steroid.

Table 3
ACAAI–ACOG recommendations for pharmacological step therapy of chronic asthma during pregnancy^a.

Category	Step therapy
Mild intermittent	Inhaled β_2 -agonists as needed (for all categories) ^b
Mild persistent	Inhaled cromolyn Substitute inhaled corticosteroids ^c if above not adequate
Moderate persistent	Inhaled corticosteroids ^c Continue inhaled salmeterol in patients who have shown a very good response prior to pregnancy Add oral theophylline and/or inhaled salmeterol for patients inadequately controlled by medium-dose inhaled corticosteroids
Severe persistent	Above + oral corticosteroids (burst for active symptoms, alternate-day or daily if necessary)

^a Based on the recommendations of the National Asthma Education Program Report of the Working Group on Asthma During Pregnancy [24]. Adapted from reference [6].^b Most published human data using albuterol, metaproterenol, or terbutaline.^c Beclomethasone or budesonide if inhaled corticosteroids are initiated during pregnancy; continuation of other inhaled corticosteroids if patient was well controlled by it prior to pregnancy; consider budesonide if patient required high-dose inhaled corticosteroids for adequate control.

7. Studies evaluating the safety of asthma medications during pregnancy

Studies evaluating the safety of asthma medications during pregnancy have focused on the effect of medication groups on the risk of congenital malformations, and certain fetal outcomes such as fetal growth, including low birth weight, mean birth weight, and being small for gestational age (weight ≤ 10 th percentile for that gestational age). However, studies that evaluate fetal growth as an outcome should also include morphometric components of fetal growth such as measurements of birth length and head circumference. Table 4 summarizes these findings by drug group.

7.1. Bronchodilators: β -adrenergic agonists

The principal action of β -agonists is to relax smooth muscle by stimulating cyclic AMP and producing functional antagonism to bronchoconstriction. All short-acting selective β -agonists currently marketed in the US received an FDA pregnancy risk category of "C". Animal toxicology experiments do not indicate any particular reproductive issues for mother or fetus. As shown in Table 4, none of the human case studies report any effect of β -agonists on reduced birth weight or an increase in the rate of low birth weight or IUGR in pregnancy. They are also not associated with congenital malformations.

However, it should be pointed out that all patients with persistent asthma require a controller medication such as an inhaled steroid. Thus, while the use of β -agonists alone appears to be safe during pregnancy, they are most often used in conjunction with other medications and their concurrent use during pregnancy may confound these results. For example, one study reported that regular use of β -agonists as rescue medication were reported to require more oral steroids and visits to the emergency room for treatment than patients who use this medication intermittently [22]. This implies that poorly controlled asthma, as well as concomitant medications, may be a confounder for interpreting perinatal outcomes in patients who use β -agonists regularly.

Long-acting β -agonists are now recommended to be used in conjunction with inhaled steroids. The use of these long-acting bronchodilators as monotherapy was reported in one study that did not find any evidence of an effect on fetal growth in humans [34].

7.2. Controller medication: inhaled corticosteroids

The most effective medication to control airway inflammation is inhaled corticosteroids. This is true across the spectrum of severity for asthma. They have a broad range of actions on the inflammatory process which may account for their ability to serve as preventive treatment for asthma symptoms, improve lung function, decrease airway hyperreactivity and asthma exacerbations. There are currently seven corticosteroids marketed globally for the treatment of asthma. These include beclomethasone dipropionate, triamcinolone acetonide, flunisolide, fluticasone propionate, budesonide, mometasone, and ciclesonide. All of them except budesonide are assigned category "C" designation by FDA. Since more human gestational data have been published for budesonide, it remains the only corticosteroid assigned to the "B" category [32,35]. The use of budesonide in early pregnancy did not cause any clinically significant effects on fetal growth or malformations. Furthermore, data from the Registry for Allergic and Asthmatic Pregnant Patients failed to find any significant relationships between the use of five different inhaled steroids (beclomethasone, triamcinolone, budesonide, fluticasone, or flunisolide) during pregnancy and perinatal

Table 4
Effect of asthma medication on perinatal outcomes^a.

	Association	Low BW	Mean BW	SGA	Congenital malformations
Short-acting β_2 agents	Positive association	None	None	None	None
	No association	3 published studies [38,42,43]	2 published studies [37,42]	4 published studies [34,37,38,42]	3 published studies [12–14]
Inhaled steroids	Positive association	None	2 published studies [35,36]	None	None
	No association	3 published studies [38,42]	1 published study [37]	4 published studies [36–38,42]	2 published studies [13,43]
Oral steroids	Positive association	3 published studies [38,40,42]	1 published study [37]	None	4 published studies [12–15]
	No association	None	None	4 published studies [34,37,38,42]	None
Cromones	Positive association	2 published studies [40,41]	None	None	4 published studies [6,7,39,42]
	No association	2 published studies [39,42]	None	2 published studies [39,42]	2 published studies [7,42]
Theophylline	Positive association	None	None	None	1 published study [6]
	No association	2 published studies [39,42]	None	3 published studies [34,39,42]	None
Leukotriene antagonist	Positive association	None	None	None	None
	No association	None	None	1 published study [34]	None

^a Adapted from reference [7] with permission.

outcomes such as reduced birth weight or small for gestational age [36]. Comparable findings concerning the lack of effect on fetal growth were reported by Organization of Teratology Information Services (OTIS) for the use of beclomethasone, budesonide or fluticasone during pregnancy even at high doses [37]. These findings lead to the following conclusions: the risk of asthma exacerbations associated with pregnancy can be reduced and lung function improved with the use of inhaled corticosteroid therapy; inhaled corticosteroids have not been shown to be associated with increased incidence of congenital malformations or adverse effects on fetal growth or other perinatal outcomes.

7.3. Oral (systemic) corticosteroids

The use of oral corticosteroids by asthmatic women during pregnancy is recommended if asthma symptoms are not controlled by high dose inhaled corticosteroids alone or in combination with long-acting β -agonists [2]. Oral corticosteroids are effective in treating poorly controlled asthma but have been associated with an increased risk of adverse perinatal outcomes including gestational diabetes, preeclampsia, preterm delivery, major congenital malformations, and impaired fetal growth [34,37–39]. Therefore, their use in pregnancy requires a careful benefit/risk assessment. They have been assigned to pregnancy category “C” by FDA. The results of studies assessing the effects of oral steroids during pregnancy have been inconsistent, with some studies showing no effect on perinatal outcomes, while others have found an increased risk of low birth weight and reduced mean birth weight [34,38,40]. When corrected for confounding factors, oral corticosteroid use was significantly associated with birth weights <2500 g (OR 1.8; 95% CI 1.1–2.9) [38]. Some studies have found a substantial increased risk (estimated excess risk of 0.2–0.3%) for isolated cleft lip with or without cleft palate, with oral steroid use during the first trimester of pregnancy. The finding of an increased incidence of both preterm and low birth weight infants may be confounded by the effects of severe or uncontrolled asthma. Despite this, because severe asthma has been associated with maternal and/or fetal mortality, risk/benefit considerations favor the use of oral corticosteroid medication when indicated in the long-term management of severe asthma during pregnancy.

7.4. Chromones (cromolyn and nedocromil)

These drugs have anti-inflammatory activity but due to their relatively limited efficacy, they are labeled to be used in mild persistent asthma in pregnant women [24]. The reports are mixed as to whether or not adverse perinatal outcomes such as increased risk for low birth weight or small for gestational age have been reported. In one study, 151 women exposed to cromolyn in the first trimester or in 243 women exposed to it at various times during pregnancy [40]. However, two other publications evaluating older cromones did indicate some risk of adverse perinatal outcomes with these drugs. While animal and human experience suggest little potential for fetal harm from cromolyn, because its efficacy data indicates that it is much less effective than inhaled corticosteroids, it is recommended as an alternative and not preferred as treatment for mild persistent asthma.

7.5. Leukotriene modifiers

Leukotriene modifiers are considered to be anti-inflammatory agents whose efficacy is much less than that of inhaled corticosteroids. There are two pharmacologic classes of leukotriene modifiers which are newer controller medications: leukotriene receptor antagonists (montelukast and zafirlukast) and 5-lipoxygenase pathway inhibitors (zileuton). Data from experimental animals did not reveal any reproductive issues for mother or fetus. The FDA has assigned these drugs to pregnancy category “C”. There are minimal human data on the use of leukotriene modifiers during pregnancy [34]. These inhibitors are generally well tolerated in non-pregnant patients. However, while zileuton has been shown to be effective for mild persistent asthma, it is not recommended for use in pregnancy. The leukotriene receptor antagonists are not as effective as steroids and are only recommended for patients who had a favorable response to them before becoming pregnant. They are an alternative to inhaled corticosteroids, and are not preferred as a treatment option in mild persistent asthmatics during pregnancy.

7.6. Theophylline

Theophylline is a methylxanthine that has bronchodilating activity and mild anti-inflammatory properties. It has been used

safely for decades during pregnancy [34,38,42,43]. None of the studies have found any adverse effects on any measures of fetal growth with drug exposure during pregnancy. Low dose theophylline (serum concentrations must be monitored closely) is considered as an alternative, but not a preferred therapy, for mild persistent asthma during pregnancy. For moderate to severe asthma, theophylline may be considered as an alternative (but not preferred therapy) adjunctive long-acting bronchodilator therapy when inhaled corticosteroids alone do not provide adequate control of the patient's asthma.

8. Conclusions

This paper reviewed the effect of maternal asthma and its management on maternal and perinatal growth. The literature documents the adverse effects of asthma on both maternal and fetal outcomes including low birth weight, perinatal mortality, preterm birth, preeclampsia, hypertensive disorders, mother/baby mortality, uterine hemorrhage, and gestational diabetes. The more severe or uncontrolled the asthma, the greater the risk of these adverse outcomes. In some reports, it has been difficult to differentiate the effects of severe uncontrolled asthma from the side effects of the medications used to treat the patients. Because acute severe asthma has been shown to be associated with maternal and/or fetal mortality, data has been generated to show that controlling asthma during pregnancy and avoiding hospitalization for asthma exacerbations leads to fewer adverse perinatal outcomes. Evaluation of most of the medications used to treat asthma have been shown to have no or minimal effects on fetal growth, and the rate of perinatal complications are reduced when maternal asthma is appropriately treated. However, the exception is oral corticosteroids which have been found to affect perinatal growth and congenital malformations.

The development of new anti-asthma drugs by pharmaceutical sponsors is difficult in this day and age because most of the asthma market is satisfied by medications directed toward patients with mild to moderate disease severity for whom there are very effective controller and reliever medications available that have been shown to be safe for use in pregnancy. The high unmet need in the asthma market is in the severe asthma patient population who responds less well to these medications due to distinct phenotypes with different inflammatory patterns and mechanisms requiring more specific targeted therapy. In addition, they have varying degrees of corticosteroid resistance, non-compliance, and the need for polytherapy. Pharmaceutical sponsors have been developing new biologicals to target more specific parts of the inflammatory cascade in these more severe patients. The antibodies are directed against inflammatory cytokines themselves, their receptors, or their signaling pathways. These antibodies are generally well tolerated, and because they cross the placenta later in pregnancy, are less of a threat to harm the fetus. In contrast, small molecules cross the placenta during the first trimester when development occurs and therefore are under more scrutiny from regulators since their benefit/risk is going to be less. One way to lessen systemic exposure of an agent to mother and fetus during pregnancy is to develop and inhaled medication which delivers the drug directly to the target area and in this way, systemic exposure is less and the benefit/risk improves.

As mentioned above, managing pregnant asthmatics requires a careful benefit/risk analysis. To aid physicians in decision-making regarding managing patients with asthma during pregnancy, there are on-line data bases such as Teratogen Information Systems (TERIS) available at <http://depts.washington.edu/~terisweb/teris/>; Reprotox, available at <http://reprotox.org/>; as well as the Organization of Teratology Information Specialists, available at

<http://www.otispregnancy.org> to help with the management of asthma during pregnancy.

Conflict of interest

Dr. Rocklin is employed by Sanofi-aventis.

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