Use of Asthma Medication During Gestation and Risk of Specific Congenital Anomalies

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KEYWORDS

• Asthma medication • Congenital anomaly • Pregnancy

KEY POINTS

- Inhaled corticosteroids and long-acting β-agonists are safe in pregnancy.
- Low priority should be placed on stepping down treatment until after delivery in a well-controlled patient.
- Good education before and during pregnancy is important to ensure compliance to asthma medication.
- More data on the use of biological therapies for asthma in pregnancy is needed.

INTRODUCTION

Asthma is one of the most common medical conditions to affect pregnancy with a prevalence of between 5% and 13% of pregnancies,[1–3] with prevalence increasing in recent years in the United States.[4,5] Poorly controlled maternal asthma during pregnancy is common, affecting up to 28% of pregnancies,[1] and can affect maternal health (preeclampsia) and neonatal outcomes (congenital anomalies, preterm delivery, increased perinatal mortality, low birth weight).[5,6] These complications can potentially be reduced with appropriate management of asthma and its exacerbations during pregnancy.[7,8]

The treatment of asthma during pregnancy follows the same principles as asthma management in the general adult population with asthma medications divided into rescue therapy and maintenance therapy.[9,10] Using a stepwise approach to asthma therapy ensures the lowest amount of medication necessary is used to control the

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patient's symptoms, with increasing number and dosage of medications with increasing asthma severity. However, one of the biggest challenges in managing asthma during pregnancy is medication adherence, and despite clear guidelines, many women remain concerned about a potential negative effect of treatment on their unborn child. A cross-sectional study by Al Ghobain and colleagues[11] investigated the views of pregnant women with asthma and found that 46.8% of pregnant asthmatic women had stopped (or expressed a desire to stop) their asthma medications during pregnancy, and 48% believed asthma medications would harm them and their babies. Powell and colleagues[12] previously found pregnant women with asthma overestimated the teratogenic risk of asthma medications with 42% perceiving a teratogenic risk with oral corticosteroids (OCSs), 12% a risk with inhaled corticosteroids (ICSs), and 5% a risk with short-acting β-agonists (SABAs). Despite women's concerns regarding the risk of asthma medications during pregnancy, the benefit of asthma education cannot be underestimated with only 40% of women more likely to continue their asthma medication during pregnancy if their obstetrician alone recommended it.[13] There is also evidence of suboptimal management of asthma within primary care. An Australian anonymous mail survey of 174 general practitioners found 25.8% of respondents would stop or decrease patients' ICS dose during pregnancy, even if asthma was well controlled on current therapy, and 12.1% of respondents indicated they did not know how to manage a deterioration of asthma during pregnancy.[14]

The overall risk of congenital abnormalities with maternal asthma is slightly increased; however, there is a lack of consensus concerning the effects of asthma medications versus the disease itself on the development of congenital anomalies because confounding factors can contribute to some of these associations.[15–17] Maternal asthma exacerbations during the first trimester of pregnancy significantly increase the risk of congenital abnormalities (adjusted odds ratio [AOR] = 1.48; 95% confidence interval [CI], 1.04–2.09), because this is a critical period of embryogenesis when congenital anomalies happen.[18] Treatments that maintain asthma control during pregnancy are favorable to optimize both maternal and fetal health, and the risk of poor asthma control greatly outweighs the risk of treatment side effects, particularly with regard to congenital anomalies.

Congenital Anomalies: Definition, Detection, and Risk Factors

Congenital anomalies may be detected prenatally, at birth, or later in infancy such as hearing or visual anomalies. In recent decades there have been major improvements in congenital anomalies diagnosis because prenatal ultrasonography has become a standard part of prenatal care, with prenatal diagnosis of structural malformations of most organ systems detectable during pregnancy.[19]

Different congenital anomalies and patterns are due to a teratogenic insult at particular gestational stages (**Fig. 1**). After the egg is fertilized and before implantation, the result of a teratogenic insult is an all or nothing effect. The first 8 weeks of pregnancy, often before the first identification of pregnancy, is termed blastogenesis (weeks 0–4) and organogenesis (weeks 4–8), when the embryo develops into tissues and organs. Insults during blastogenesis can result in severe, often lethal anomalies that involve several organ systems. Insults during organogenesis tend to involve single organ structures; for example, weeks 3 to 5 are critical for central nervous system development, and weeks 7 to 9 for urogenital development. During the fetal period (after 8 weeks gestation), harmful influences may affect fetal growth and function (eg, hearing loss, cognitive impairment, lung immaturity). Therefore, timing of exposure of a particular event or insult, duration and frequency of exposure, can result in very different outcomes.

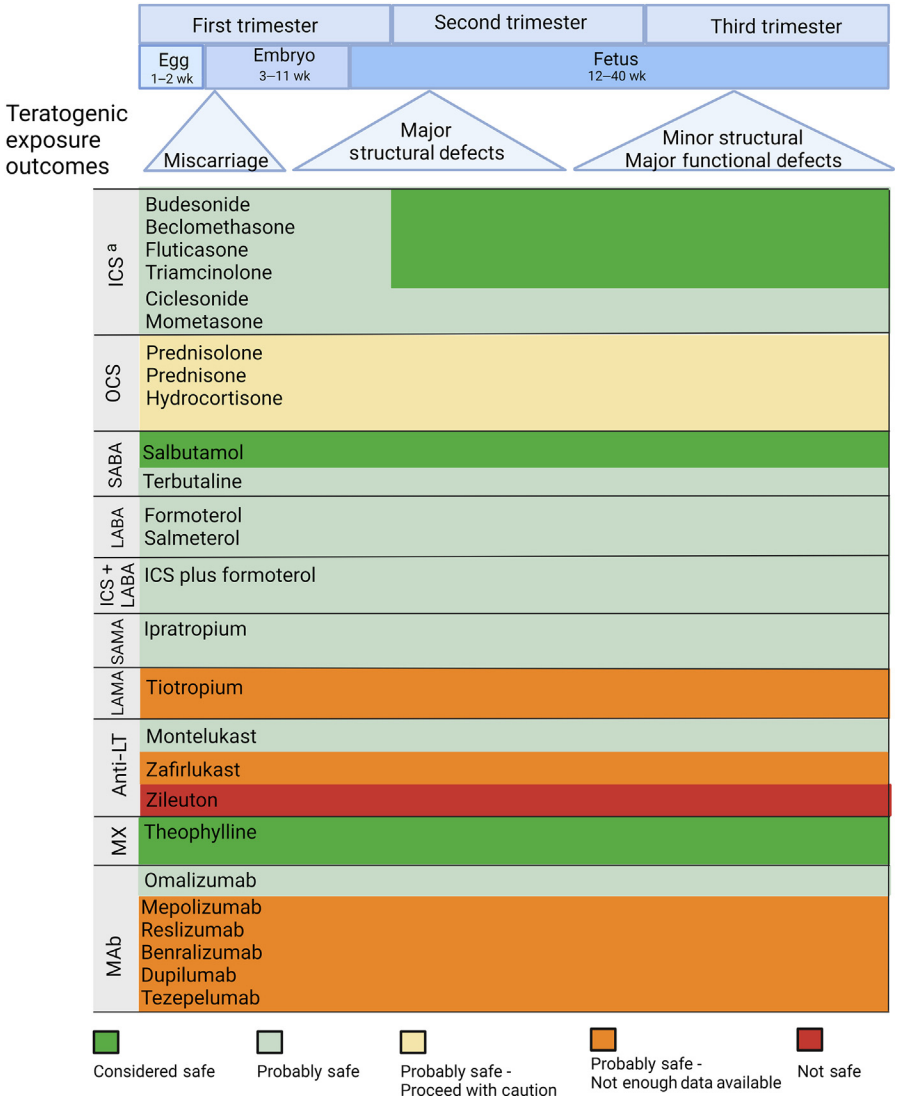

Fig. 1. Risk of teratogenic outcomes with asthma treatment. LAMA, long-acting muscarinic agonist; LT, leukotriene; mAb, monoclonal antibody; MX, methylxanthine; SAMA, short-acting muscarinic antagonist. [a]High-dose ICS (>1000 μg/d beclomethasone equivalent) in the first trimester could be associated with a small increased risk of congenital anomaly.

The risk factors for developing anomalies can be classified as modifiable (environmental, smoking, obesity, diabetes, medications, folic acid deficiency) and nonmodifiable (genetic), although in most cases the cause remains unknown. A genetic predisposition to specific teratogens has been studied extensively. Maternal and fetal genetic variants have been associated with an embryo's susceptibility to develop fetal alcohol syndrome.[20] Cigarette smoke exposure is a risk factor for the development of orofacial clefts and gastroschisis in the fetus; however, the risk is increased even further if the fetus carries specific, rare genotypes.[21,22] Specific medications are

known teratogens. For example, methotrexate due to its role as a folic acid antagonist leads to microcephaly, cardiac effects, and limb anomalies[23]; lithium use in early pregnancy is associated with cardiac anomalies[24]; and phenytoin causes major malformations including facial clefts and cardiac disease.[25] Although it is preferable that all pregnant women refrain from taking any medications during pregnancy, this is not always possible, and therefore, primary prevention within the whole population by controlling environmental risk factors and ensuring optimum preconceptual care is a crucial health care priority.

Safety of Asthma Medications During Pregnancy

Pregnant women are generally excluded from clinical trials due to a lack of safety information on most medications in pregnancy; therefore knowledge regarding safety for the fetus is usually presented from large population studies (**Table 1**). Thus, existing information is usually limited, and more studies are required due to lack of information or potential confounders. Unfortunately animal studies are not always predictive of teratogenic effect in humans,[26] as observed with thalidomide, which was approved for use outside the United States for pregnant women suffering from morning sickness in the late 1950s and the early 1960s but was found to result in limb congenital anomalies despite animal studies finding only occasional teratogenic events.[27]

The treatment of asthma during pregnancy follows the same principles as asthma management in nonpregnant patients. Asthma medications are divided into maintenance and rescue therapy. Maintenance therapies are used long term to prevent asthma symptoms and exacerbations and include ICSs, long-acting β-agonists (LABA), antileukotrienes, anticholinergic agents, theophylline, and more recently biological therapies, whereas rescue therapies, primarily rapid-onset bronchodilators such as SABAs, provide immediate relief of symptoms. Although there is a general concern about any medication use in pregnancy, an important role for a clinician is to stress the importance of maintaining good control of asthma and medication adherence while reassuring a pregnant woman of the safety of asthma medications during pregnancy. Although treatment adjustments can be made during pregnancy, the Global Initiative for Asthma (GINA) recommends that "given the evidence in pregnancy and infancy for adverse outcomes from exacerbations during pregnancy, including due to a lack of ICS or poor adherence, and evidence for safety of usual doses of ICS and LABA, a low priority should be placed on stepping down treatment (however guided) until after delivery, and ICS should not be stopped in preparation for pregnancy or during pregnancy."[9]

Inhaled Corticosteroids

ICSs have been the cornerstone of asthma therapy for more than 40 years and are recommended as a first-line therapy for asthma in both adolescents and adults, recently replacing SABAs as the first-line therapy for mild asthma.[9] However, ICS adherence during pregnancy is poor with 39% of pregnant women reporting nonadherence[28] despite studies showing that ICS does not increase risk of congenital anomalies associated with its use,[29] ICS reduces asthma exacerbations in pregnancy,[30] and cessation of ICS increases the risk of developing exacerbations, which are a risk factor for congenital anomalies rather than asthma itself (AOR = 1.21; 95% CI, 1.05–1.39).[31]

Concerns raised about a potential association of congenital anomalies and moderate- to high-dose ICSs have been examined. A previous literature review[32] summarizing the risk of congenital malformations with the use of ICSs in pregnancy found that in 15 separate studies[29,33–46] comparing women with asthma using any ICS versus women with asthma not using ICS the adjusted relative risk ranged from 0.4 to 1.1.

Table 1
Summary data for asthma medications and risk of congenital anomalies

Drug Category	Preferred Drugs	Human Data	Considerations
Inhaled corticosteroids	Budesonide (more published data) Beclomethasone (reassuring data)	At low and moderate doses no increased risk of congenital anomalies. One study showed at >1000 μg/d beclomethasone equivalent in the first trimester there was a small increased risk of congenital anomaly[47]	If well controlled on an ICS before pregnancy this may be continued because changing drug may threaten asthma control
Inhaled SABAs	Salbutamol/albuterol (more published data)	Recommended as safe in pregnancy. Large population studies have found no association between β-agonists and congenital anomalies[51]	Goal is to minimize SABA use using ICSs to ensure adequate control
Inhaled LABAs	Salmeterol Formoterol Indacaterol Vilanterol	Similar safety profile to SABAs Animal studies for once-daily LABAs are reassuring; however, no human data are available	LABA monotherapy should not be used These agents are not first choice in pregnancy unless a once-daily fixed combination regime is required to ensure adherence
Combination therapy	Low-dose ICS-formoterol can be used as maintenance and reliever therapy	The use of ICS-LABA combination did not result in a significant increased risk of congenital anomalies compared with high-dose ICS alone during the first trimester[56]	Limited studies, however, probably safe in pregnancy with no increased congenital anomaly risk
Oral corticosteroids	Prednisone (more published data)	Conflicting data; however, recent studies suggest no increased risk of congenital anomalies[58,59]	Major benefit outweighs the risk in severe asthma

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Drug Category	Preferred Drugs	Human Data	Considerations
Antileukotrienes	Montelukast (more published data)	A cohort study of 180 montelukast-exposed pregnancies found montelukast did not increase the risk of major congenital anomalies[63]	Zileuton not recommended in pregnancy due to fetal abnormalities in animal studies.[61] Montelukast probably safe as an add-on therapy in uncontrolled asthma
Anticholinergics	Ipratropium	Nebulized ipratropium recommended for acute, severe asthma not responding to β-agonists alone	No published data for tiotropium in pregnancy
Theophylline	N/A	No increased risk of congenital anomalies compared with inhaled beclomethasone; however, increased risk of discontinuation due to side effects[38]	No evidence of teratogenic effects. Blood levels should be monitored
Monoclonal antibody therapies	Omalizumab	No increased risk of congenital anomalies with omalizumab[69]	Probably safe in pregnancy; however, larger studies are needed
	Mepolizumab	No published human data	Pregnancy registry ongoing
	Reslizumab	No published human data	Pregnancy registry ongoing
	Benralizumab	No published human data	Pregnancy registry ongoing
	Dupilumab	A review of 23 pregnancies in study patients found no increased risk of congenital anomalies; however, low numbers of pregnancies, therefore more data needed[78]	EMA states dupilumab should only be used during pregnancy if the potential benefits outweigh the risks.[81] Pregnancy registry ongoing
	Tezepelumab	No published human data	No pregnancy registry

Abbreviations: EMA, European Medicines Agency; LABA, long-acting β-agonist; N/A, not applicable.

Bakhireva and colleagues[35] were the only investigators to report a significantly increased risk of congenital anomalies associated with ICS use when they compared 438 pregnant women using ICSs during pregnancy with nonasthmatic control pregnant women (4.1% vs 0.3% presence of major anomalies, respectively, $P = <0.05$). Blais and colleagues[47] studied 13,280 pregnancies in women with asthma and found 1633 congenital anomalies, the most frequent being cardiac and musculoskeletal. High daily ICS use (>1000 μg/d beclomethasone equivalent) during the first trimester was associated with a significant risk of congenital anomalies (AOR = 1.63; 95% CI, 1.02–2.60), compared with women taking low- or medium-dose ICSs. These results must be interpreted with caution, however, because the number of women taking high-dose ICSs was small (n = 154, 1.1%), and the results were based on medication claims and not actual usage. Furthermore, the investigators could not out rule asthma severity, age, or socioeconomic group confounding the results. However, with respect to the first trimester, women who abstained from ICS use had a higher risk of congenital anomalies in their baby compared with women who used low- or moderate-dose ICS, supporting the belief that uncontrolled maternal asthma rather than ICS is associated with congenital anomalies. In addition, the ICS budesonide has been studied extensively in pregnancy with a large body of safety data showing no increased risk of congenital anomalies or stillbirths[34,48,49] and is considered first-line ICS if commencing therapy during pregnancy; however, if a patient is well controlled on an ICS before pregnancy this may be continued because changing formulations may threaten asthma control.

β-Agonists

SABAs provide symptom relief by rapidly reversing the effects of bronchoconstriction in asthma and are now recommended as an add-on therapy for patients taking ICSs.[9] LABAs are the second most widely used controller medication in asthma and compared with SABAs they provide more prolonged bronchodilation, with a greater reduction in symptoms, increased lung function, and reduced need for SABAs. SABAs are recommended as safe in pregnancy.[10] LABAs when used alone have previously been associated with increased asthma-related mortality in general,[50] and therefore they are only recommended as an add-on controller therapy in fixed-dose combination with ICSs to treat moderate to severe asthma.

A study examining more than 76,000 registrations of congenital abnormalities raised concerns finding an association between inhaled β-agonist exposure during the first trimester and congenital anomalies including cleft palate and gastroschisis.[17] However, a larger population-based cohort study of more than 519,242 infants, including 19,513 mothers with asthma medication exposure, found no significant association between inhaled β-agonists and cleft palate (AOR = 1.05; 95% CI: 0.44–2.51) or gastroschisis (AOR = 1.08; 95% CI, 0.37–3.15),[51] suggesting no association between β-agonists and congenital anomalies. A systematic review of 21 published studies that examined β-agonist use and congenital anomalies[52] found only 1 study that reported a significant risk of congenital anomalies with LABA, whereas 4 studies found a significantly higher risk of congenital anomalies with SABA and 1 reported a significantly lower risk of congenital anomalies with SABA. The investigators state, however, these results must be interpreted with caution because all studies except 2 used nonasthmatic women as the reference group, which could have confounded the underlying asthma disease and the effect of medication, and further studies are required.

Inhaled salbutamol is considered the first-line SABA therapy for pregnant women because it has been studied most extensively.[29] There is no preferred LABA therapy in pregnancy, and a previous study showed no difference in perinatal complications

between salmeterol or formoterol exposure; however, congenital anomalies were not specifically examined.[53] Therefore, the goal of asthma management in pregnant women is to minimize the use of SABAs using ICSs, and if required, adding a LABA, to ensure adequate control and prevent severe exacerbations known to increase the risk of congenital anomalies. Ultra-LABAs (eg, indacaterol and vilanterol) are newer LABAs used in a once-daily fixed combination with ICSs. Although animal studies for ultra-LABAs suggest low risk of congenital anomalies, no human data are available. Thus, these agents are not our first choice in pregnancy unless a once-daily fixed combination regime is required to ensure adherence.

Combination Therapy

Asthma management for adolescents and adults is based on a stepwise approach. When asthma cannot be controlled with low-dose ICS alone, guidelines suggest adding LABA in a fixed-dose inhaler or increasing the ICS dose to the medium range.[9] As needed low-dose ICS-formoterol is now recommended as the first-line therapy for mild asthma instead of SABA[9] because it has been associated with reduced asthma exacerbations and improved peak flows and forced expiratory volume in the first second of expiration compared with as-needed SABA.[54] ICS-formoterol combination can also be used as a maintenance and reliever therapy and is effective at reducing exacerbation risk, and results in a simplified approach to asthma management.[55]

Pregnant women were excluded from clinical trials assessing the safety of ICS-formoterol combination therapy as needed and as a maintenance and reliever therapy, limiting our knowledge of safety in pregnancy. Physician's and patient's perception of medication risk of teratogenicity due to lack of clinical trial evidence for these agents may result in them changing treatment regimen during pregnancy. A Canadian retrospective cohort study of 1302 asthmatic pregnant women assessed the risk of congenital malformations in women using ICS-LABA combination versus high-dose ICS alone in the first trimester.[56] The use of ICS-LABA combination had a similar risk of congenital anomalies compared with high-dose ICS alone during the first trimester (AOR = 1.0; 95% CI, 0.6–1.7) in moderate to severe asthma. These results are reassuring and suggest that ICS-LABA combination therapy is safe in pregnancy with no increased congenital anomaly risk, and should provide reassurance to both women and physicians to continue their asthma combination medication during pregnancy.

Oral Corticosteroids

OCSs may be required for the treatment of acute exacerbations or used at low dose for management of persistent severe asthma. There are more data regarding the safety of prednisone for pregnant women because it has been studied more extensively.

There are conflicting data regarding the risk of congenital anomalies and OCS in pregnancy. Park-Wyllie and colleagues[57] performed a meta-analysis of 10 studies showing an increased risk of orofacial anomalies when OCS is used during the first trimester only (odds ratio [OR] = 3.35; 95% CI, 1.97–5.69). These results must be interpreted with caution because 7 studies included women with various underlying conditions requiring OCS use, whereas three studies did not describe the mother's indication for OCS. And this could have resulted in confounding, therefore further studies are required assessing the effect of OCS in asthma alone during pregnancy. Reassuringly data from the National Birth Defects Prevention Study of 1304 congenital anomaly births in women who reported any asthma medication use from 1997 to 2011 found no increased risk of cleft lip and prednisone use.[58,59] As a previous study found

an association between first-trimester severe asthma exacerbation requiring hospitalization and congenital anomalies when compared with women with asthma who did not require a visit to the emergency department or hospitalization (OR = 1.64; 95% CI, 1.02–2.64),[60] the benefit of OCSs in the prevention of severe asthma exacerbations outweighs the potential risk of congenital anomalies associated with their use.

Antileukotrienes

Montelukast and zafirlukast are selective leukotriene receptor antagonists (LTRAs) indicated as maintenance controller therapies for asthma. Although data for the use of both agents are limited in pregnancy, montelukast is the first-line LTRA therapy during pregnancy because it has been studied most extensively. Zileuton is a leukotriene synthesis inhibitor that is not recommended in pregnancy due to fetal abnormalities in animal studies[61] with no evaluation of safety in human pregnancy.

Montelukast is indicated as an add-on therapy for asthma; however, a Danish cross-sectional observational study through a prescription-based database attempted to realize the risk of congenital abnormalities associated with montelukast in pregnant women when used as a single agent (n = 401) compared with its use simultaneously with other asthma medications (n = 426) during the first trimester of pregnancy.[62] Rates of major congenital anomalies were not different in the montelukast-only group (AOR = 1.4; 95% CI, 0.9–2.3) when compared with montelukast simultaneously with other asthma medications (AOR = 1.0; 95% CI, 0.6–1.8) or when compared with other asthma medications alone (AOR = 1.1; 95% CI, 1.0–1.2). This study did have several limitations because the number of congenital anomalies was low (16 in the montelukast alone group) reducing the statistical power. The study did not have sufficient power to look for associations with specific anomalies, the database did not include information regarding the pregnant women's indication for montelukast, and the extraction of information from a prescription database may be a poor proxy for actual use of medications. A separate prospective cohort study of 180 montelukast-exposed pregnancies reported the same findings that montelukast did not increase the risk of major congenital anomalies.[63] Although data about effects of montelukast on congenital abnormalities during pregnancy are limited, when combined these reports consistently suggest that montelukast is probably safe as an add-on controller medication to achieve good symptom control in pregnancy.

Anticholinergics

Anticholinergic agents include the short-acting muscarinic antagonist (SAMA) ipratropium and long-acting muscarinic antagonists (LAMAs) including tiotropium. Anticholinergics induce bronchodilation through the inhibition of muscarinic receptors in smooth muscle. LAMAs are recommended as add-on therapy for moderate to severe persistent asthma, due to their ability to reduce asthma exacerbations and improve asthma control.[64] Nebulized ipratropium with β-agonists has been recommended for the management of acute, severe asthma not responding to β-agonists alone.[65] No well-controlled clinical studies of tiotropium have been specifically performed in pregnant women.

Theophylline

Theophylline previously was a cornerstone of asthma medication because of its bronchodilator and anti-inflammatory activity; however, its use has decreased in recent decades due to the introduction of ICSs and concerns regarding its toxicity and side effect profile.[66] Thus, theophylline is no longer recommended as a first-line therapy for asthma and is only recommended as an alternative add-on controller therapy for

moderate to severe asthma. Theophylline has previously been used in the treatment of asthma during pregnancy with no evidence of teratogenic effects; however, pregnant women were significantly more likely to discontinue theophylline than inhaled beclomethasone due to increased rate of side effects (6 of 194 discontinued in the beclomethasone group, 17 of 190 in the theophylline group; $P = 0.016$).[38] During theophylline treatment in all adults, however, blood levels should be monitored because the risk of toxic reactions increases when the serum theophylline level is higher than the therapeutic range of 10 to 20 μg/mL.[67]

Anti-IgE Therapy

Omalizumab is a recombinant monoclonal anti-IgE antibody that binds specifically to free human immunoglobulin E (IgE) in the blood and is approved as an add-on therapy for the treatment of moderate to severe allergic asthma despite adequate ICSs.[9] Animal studies using subcutaneous doses of omalizumab up to 10 times the maximum human dose found no evidence of fetal harm in cynomolgus monkeys.[68]

The Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy Trial (EXPERT) examined the association between omalizumab and congenital anomalies in 230 pregnancies to compare exposed pregnancies with a disease-matched population of pregnant women with moderate to severe asthma.[69] The rates of major congenital anomalies were similar in both groups (8.1% in the omalizumab-exposed group vs 8.9% in the unexposed group) with the most common major congenital anomalies in the exposed group being torticollis (2.2%), hydronephrosis (1.3%), and hypospadias (0.9%), and the most common major congenital anomalies in the unexposed group being cardiac (2.8%), musculoskeletal (1.2%), and urinary system (1.1%) anomalies with no unique system anomaly found within the exposed group alone. Therefore, this study does provide reassurance regarding the lack of teratogenic risk of omalizumab and the safety of continued use of omalizumab in women with improved asthma control and reduced exacerbations before pregnancy. Therefore, for women established on omalizumab before pregnancy, if the benefits outweigh the risks, omalizumab therapy may be continued; however, it is not currently recommended to start omalizumab in pregnant women.

Anti-Interleukin-5, Anti-Interleukin-4/13, and Anti-Thymic Stromal Lymphopoietin Monoclonal Antibody Therapies

Interleukin (IL)-5 is a key cytokine involved in the recruitment, activation, and survival of eosinophils, and anti-IL-5 biological therapies reduce eosinophilic inflammation by inhibiting this pathway.[70] There are 3 monoclonal antibody (mAb) anti-IL-5 therapies that are approved for use in severe eosinophilic asthma uncontrolled despite maximal therapy (high-dose ICS or medium-dose ICS-LABA, and 2 or more exacerbations per year requiring OCS or chronic OCS use): mepolizumab and reslizumab, which bind to IL-5 preventing it from binding to its receptor on eosinophils, and benralizumab, which binds to the α subunit of the IL-5 receptor resulting in direct and rapid near depletion of eosinophils. Animal studies of mepolizumab (monkeys),[71] reslizumab (mice and rabbits),[72] and benralizumab (monkeys)[73] found no teratogenic effects. The safety and efficacy of all 3 anti-IL-5 agents in pregnant women is unknown because pregnancy was an exclusion criterion for all the clinical trials, and pregnancy registries are ongoing.

Dupilumab is an mAb that binds to the α subunit of the IL-4 receptor blocking signaling of both IL-4 and IL-13, which are key cytokines in type 2 airway inflammation. Dupilumab has been approved by the US Food and Drug Administration for the treatment of atopic dermatitis and severe oral steroid-dependent asthma. Animal studies of dupilumab up to 10 times the maximal human dose in cynomolgus monkeys found

no fetal harm.[74] Three case reports of dupilumab used safely in the treatment of atopic dermatitis in pregnancy have been reported with no adverse fetal outcomes.[75–77] Pregnancy was an exclusion criterion for all the clinical trials of dupilumab, therefore the safety and efficacy in pregnant women is unknown. The European Medicines Agency completed a review in 2017 that reported 23 pregnancies in study patients treated with dupilumab resulting in 8 healthy births (1 twin birth), 2 induced abortions, 6 spontaneous abortions (with 2 of these 6 cases having at least 1 risk factor for abortion), 5 ongoing pregnancies, and 3 pregnancies lost to follow-up.[78] The risk of spontaneous abortion in pregnancy was similar to that of the general population (11%–24%).[79,80] The risk of medication-associated congenital anomalies could not be determined, however, due to the low numbers of pregnancies. The EMA report stated that dupilumab should only be used during pregnancy if the potential benefits outweigh the potential fetal risks.[81] A pregnancy registry for dupilumab in pregnancy is ongoing.

Thymic stromal lymphopoietin (TSLP) is a cytokine produced by the epithelium in response to external stimuli including viruses, bacteria, and allergens and drives allergic inflammation early in the inflammatory cascade and may be more suitable for a broader severe asthma population due to its earlier activity within the inflammatory cascade.[82] Tezepelumab is a human anti-TSLP immunoglobulin that binds to human TSLP and prevents interaction with its receptor[83] and has recently been granted approval by the US Food and Drug Administration for patients with severe asthma.[84] A randomized, double-blind, placebo-controlled study assessed the effect of tezepelumab on annualized rate of asthma exacerbations for patients with severe asthma with 2 or more asthma exacerbations in the year prior despite the use of medium- or high-dose ICSs and at least 1 additional controller medication, with or without OCSs.[85] The trial showed that annual asthma exacerbation rate was significantly reduced in the tezepelumab group compared with the placebo group (0.93; 95% CI, 0.8–1.07 with tezepelumab compared with 2.10; 95% CI, 1.84–2.39 with placebo; $P < 0.01$), with a significant reduction in exacerbations observed in the tezepelumab group irrespective of baseline blood eosinophil levels. These results were observed independent of baseline blood eosinophil count or other T2 inflammatory biomarkers. Pregnancy was an exclusion criterion for all studies to date; therefore no safety data are available. Animal studies of tezepelumab in cynomolgus monkeys up to 168 times the maximal human dose found no fetal harm.[84] A pregnancy registry for tezepelumab is yet to be created.

Given the lack of human data for anti-IL-5, anti-IL-4/13, and anti-TSLP biologics and the risk of teratogenic events, physicians prescribing these medications to women of reproductive age or pregnant should inform the woman regarding the potential effects of biologics on pregnancy and risks of congenital anomalies.

DISCUSSION

Managing asthma to control the underlying disease and optimizing fetal outcomes during pregnancy is a challenge, particularly in severe disease. Asthma may adversely affect both maternal quality of life and perinatal outcomes including congenital anomalies. Optimal management of asthma during pregnancy is imperative to reduce fetal risk of congenital anomalies associated with severe exacerbations. Owing to the increasing prevalence of asthma worldwide, it is imperative that physicians are aware of the potential teratogenic effect severe asthma with exacerbations can have on a developing fetus, as well as the potential teratogenic risk of antiasthma medications, to allow physicians determine the optimal therapy for their pregnant patient and ensure the pregnant women is educated regarding the importance of continuing

therapy during pregnancy. Most human clinical drug trials exclude pregnant asthmatic women, thereby limiting our knowledge of the effect asthma medications can have on the developing fetus. This phenomenon is not unique to asthma, however, because more than 80% of pregnant women are prescribed at least 1 prescription or over-the-counter medication during pregnancy.[86] The lack of clinical trials in pregnant women with asthma can result in pregnant women and health care workers overestimating the teratogenic risk of asthma medications. A core part of improving the health of pregnant women is ensuring they are appropriately engaged and included in clinical research studies because this will allow future pregnant women to make evidence-based decisions regarding their disease and treatment.

Most small prospective studies showed no certain teratogenic effect of antiasthma medications. Several retrospective studies suggested associations with some specific malformations, but the scientific value of these studies is low. Some large studies demonstrated a relatively weak association between the use of antiasthma drugs and any congenital malformation and specifically ICS medications and cardiovascular anomalies and OCS and orofacial anomalies. There seems to be no specificity with regard to type of antiasthma drug, which makes it likely that a confounder such as maternal asthma or an asthma exacerbation causes anomalies most likely via hypoxia. A low priority should be placed on stepping down therapy in preparation for, or during pregnancy. Instead, pregnant women should be educated on the benefits and safety of usual controller medications particularly ICSs, and the increased risk of asthma exacerbations with poor adherence.

Women with severe asthma may require the use of biological therapies such as omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and in the future tezepelumab to control their asthma, and the risk of continuing treatment during pregnancy or even commencing treatment in unwell pregnant women with severe asthma will need to be assessed. The randomized clinical trials that supported the approval of these medications for the treatment of severe asthma excluded pregnant women, therefore prospective data regarding their safety and efficacy are limited. Observational data for omalizumab shows no association between omalizumab treatment and increased risk of congenital anomalies; however, the interpretation of these data are limited due to small sample size and the presence of confounding factors such as asthma severity on perinatal outcomes. Pregnancy registries are ongoing for mepolizumab, reslizumab, benralizumab, and dupilumab; however, there are currently no published human data available, and therefore data are lacking regarding their teratogenic risks in pregnancy. Clinicians need to be aware of the risks of severe asthma in pregnant women, and the lack of available data regarding these agents to ensure they can appropriately consider the risks and benefits of these treatments during pregnancy, and relay this information to pregnant mothers and women of childbearing age. To adequately determine the safety of these medications in pregnancy, human data are critical, therefore clinicians are encouraged to enroll women who require or receive these treatments during pregnancy into the relevant pregnancy registries. High-quality randomized controlled trials of these agents in pregnancy are also required to strengthen the evidence base and inform future guidelines for asthma management in pregnancy.

SUMMARY

Although there are concerns regarding the use of any medications during pregnancy, particularly the first trimester, the benefits of actively treating asthma and reducing the risks of exacerbations markedly outweigh the risks of congenital anomalies. Given the

evidence for adverse outcomes including congenital anomalies associated with uncontrolled asthma during pregnancy, a low priority should be placed on stepping down therapy, and ICSs should not be stopped in preparation for or during pregnancy. High-quality randomized controlled trials are required to strengthen the evidence base and inform future guidelines for asthma management in pregnancy; specifically, safety studies regarding the use of biological therapies in severe asthma in pregnancy are needed urgently.

CLINICS CARE POINTS

- The available safety data for asthma medications in pregnancy and congenital anomaly risk are overall reassuring, particularly for ICSs and β-agonists
- The risk of congenital anomalies due to severe exacerbations and poorly controlled asthma can be reduced with good asthma control
- Pregnant women overestimate the risk of asthma medications resulting in congenital anomalies
- Physicians should discuss risk and benefit of asthma medications with women to ensure they understand the risks of discontinuing asthma medications during pregnancy and the risk of asthma exacerbations resulting in congenital anomalies
- Further studies for biological therapies in pregnant women with severe asthma are needed

DISCLOSURE

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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