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LTRA Use in Pregnancy: A Systematic Review on their Safety and Association with Congenital Anomalies'

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Abstract

This systematic study seeks to assess the safety of Leukotriene Receptor Antagonists (LTRAs) and their connection with congenital abnormalities during pregnancy. Asthma is a chronic airway illness marked by inflammation and airflow restriction, and LTRAs are frequently used to treat it. Five papers were chosen for analysis after conducting a complete literature search. The findings indicate that LTRAs, such as montelukast and zafirlukast, do not represent a major teratogenic risk and are unlikely to be linked to congenital abnormalities. Infants exposed to LTRAs during prenatal development may have a slightly higher risk of congenital cardiac abnormalities. Additional research is required to ascertain the safety of LTRAs during pregnancy by pharmacokinetic and post marketing surveillance, as well as to examine the long-term developmental consequences of LTRAs. Patients with asthma who are pregnant may benefit from alternative asthma treatments such as omalizumab, beta2-agonists, and glucocorticoids. Taken cautiously and under medical supervision, LTRAs seem to be a good therapy choice for asthma during pregnancy.

Keywords: Posture, Musculoskeletal system, Lower back pain.

Introduction

Asthma is a chronic airway illness characterized by airway inflammation, hyperresponsiveness, and airflow restriction. Inflammation of the airway is characterized by the infiltration of inflammatory cells, including neutrophils, eosinophils, and lymphocytes; thus, asthma can be classified into four types based on the type of inflammatory cell found in sputum: eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic asthma phenotypes. [1] According to studies, leukotrienes play an important part in the pathophysiology of the illness; hence, leukotriene receptor antagonists are among the most commonly recommended drugs for the prevention and treatment of asthma, as well as for properly controlling the condition [2].

Leukotrienes are created by the enzyme 5-lipooxygenase of inflammatory cells in the airways, which breaks down arachidonic acid, which is mostly released from cell membrane phospholipids by phospholipase A2. There are two kinds of leukotrienes: those with amino acid moiety and those with merely hydroxyl groups. [3] The latter is referred to as chemoattractant LTB4, whereas the first is referred to as CysLTs (LTC4, LTD4, and LTE4). Leukotrienes, like other lipid mediators, have a role in signaling, namely via GPCRs. LTB4 activates BLT1 and BLT2, whereas CysLTs activate CysLT1 and CysLT2. Their affinity is rated LTD4 > LTC4 > LTE4 and LTD4 = LTC4 > LTE4, to CysLT1 and CysLT2, respectively. CysLT2 binds LTC4 and LTC4 one log less than CysLT1 [4].

LTB4 and CysLTs are both important in the pathogenesis of asthma. To begin, LTB4 acts as an inflammatory mediator, responsible for myeloid leukocyte recruitment, activation, and survival, as well as the discovery of a novel pathway that reveals the role LTB4 plays in the activation of T cells and dendritic cells, which are thought to be the primary antigen-presenting cells in the lungs [5, 6]. Furthermore, CysLTs, the most effective bronchoconstrictor, are important in asthma because they are identified in the urine, blood, and BAL fluid of asthmatic patients following bronchospasms [4, 7].

LTRAs, which target leukotriene receptors, have been shown to be beneficial in asthmatic patients. A research found that parents of asthmatic children preferred montelukast to inhalers due to its ease [8]. Because very young kids sometimes have trouble utilizing inhalers correctly, LTRAs are excellent options. The LTRAs montelukast (2 years and older), zafirlukast (5 years and older), and pranlukast (2 years and older) are recommended for children with asthma [9]. Despite these beneficial uses, studies are increasingly reporting non-psychiatric and psychiatric side effects with longer LTRA use, prompting reconsideration of the benefit/risk ratio in both pediatric and adult patient populations, emphasizing the importance of evaluating patients on LTRA medications and questioning when they are necessary. [10] Furthermore, research has focused on the use of LTRA during pregnancy because of the possible consequences on mother and fetal health, including congenital abnormalities. Previous research has consistently demonstrated that montelukast is most likely a safe medication and is the first-line therapy for asthma in pregnancy, with no risk of increasing the likelihood of congenital anomalies, as there was no difference in the rate of congenital anomalies between pregnant females receiving the medication and those who did not.

However, research on the safety of montelukast and other LTRAs during pregnancy remains lacking [11].

As a result, given the growing usage of LTRAs during pregnancy, our study seeks to offer an updated, thorough evaluation of their safety in pregnancy, particularly in terms of their relationship with the development of congenital malformations.

Methods

Database Search

A comprehensive literature search was conducted on PubMed, Cochrane, Scopus, and World of Science using appropriate and relevant key term searches, as well as Boolean operators: (leukotriene receptor antagonist OR LTRAs OR montelukast OR zafirlukast OR pranlukast) AND (fetus OR fetal OR prenatal) AND (effect OR impact OR influence OR outcome) AND (abnormalities OR anomalies OR malformations OR defects OR disorders).

After duplicates were found and eliminated, papers were rigorously independently reviewed by two writers in accordance with each study's abstract. The remaining papers were assessed separately by two authors using full-text articles, and only those that met our inclusion criteria were included in the review. Any disagreements amongst the authors were handled through talks and reference to the inclusion criteria.

Our inclusion criteria were based on the PICO (Population, Intervention, Comparator Group, and Outcome): observational study design, manuscripts written in English, pregnant females as the population, receiving LTRAs as opposed to those receiving no drugs, a placebo, or other drugs, and congenital anomalies as the outcome. Meanwhile, our exclusion criteria included any studies that were reviews, editorials, letters, or meta-analyses, were not originally written in English, had populations other than pregnant women, used other drugs as interventions, had no controlled or placebo group, or did not investigate congenital anomalies. A PRISMA flowchart was then created to emphasize the research selection process.

Data extraction

Following the inclusion of the studies that meet our inclusion criteria, a table was created to highlight the salient features of each publication. The title, first author, year, nation, research design, medications used, and a summary of the results were all documented and included in the table for each study. To the best of the authors' knowledge, there are no RCTs specifically assessing the use of LTRA in pregnancy and congenital abnormalities, hence only observational studies were included.

Quality assessment and risk of bias

The risk of bias in each of the included studies was assessed using Cochrane's RoB2 Tool, and the findings were plotted in a traffic-light diagram to guarantee the caliber of our review. Risk factors for bias analysis included randomization biases, planned intervention variations, missing outcome data, outcome measurement biases, and biases in the choice of published outcomes (**Figure 1**). shows that, overall, the included studies had a minimal risk of bias, with the exception of the research [5], with some concerns regarding randomization and deviations from intended intervention.

Additionally, methodological rigor was ensured by conducting a quality evaluation using the AMSTAR-2 tool, which consists of a series of questions to assess the caliber of the papers included in our systematic review. Our study is a moderate strength review, as shown in Figure 1 in the Supplementary Data.

Results

In the United States, [12] recruited pregnant women who were at least eighteen years old, had a physician's diagnosis of asthma, and agreed to be followed up with both during and after the pregnancy. A comparison group of asthma-free pregnant women was also included. The Organization of Teratology Information Specialists (OTIS) carried out the study as a component of the Asthma Medications in Pregnancy Study between 1998 and 2003. Medical record reviews and structured telephone interviews were used in this investigation. Structured telephone interviews were used to collect data, and follow-up interviews were held at various points during pregnancy. An outcome call was also held following delivery to collect data on the outcomes for both the mother and the fetus.

Using a clinical database, [13] carried out an observational retrospective cohort research in Japan. Healthcare experts at two Japanese medical institutions that provide pregnancy- related medication counseling conducted interviews to collect data. Pre-appointment questionnaires, confirmation interviews, and post-appointment surveys were used in this

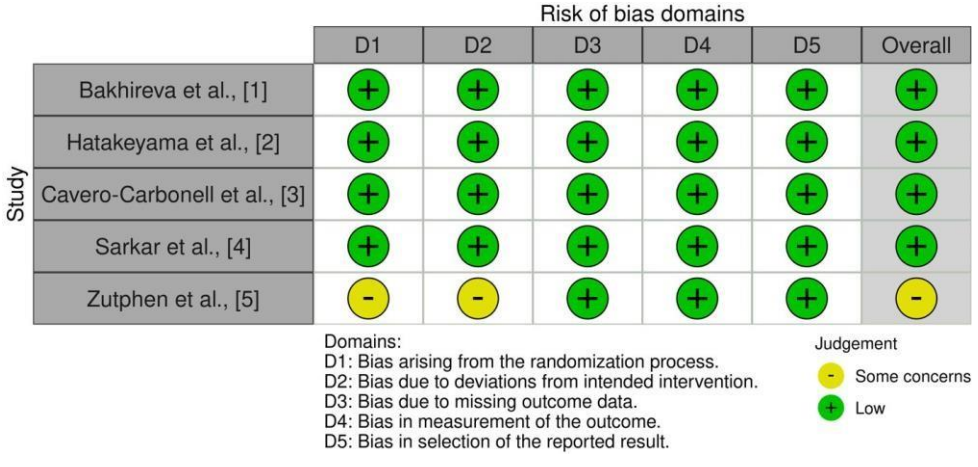

Figure 1: Risk of Bias (RoB) analysis of the included studies.

study, which ran from April 1988 to December 2017, to gather data on pregnancy outcomes around one month following birth. The study especially looked at pregnant women who took control medications from the control group throughout the first trimester of pregnancy together with montelukast, pranlukast, or zafirlukast from the LTRAs group.

Using information from Danish registries, [14] carried out a cross-sectional observational epidemiological analysis with an emphasis on pregnancies that occurred between 1998 and 2009. Through the use of personal identifying numbers, data sources were connected from the Danish Medical Birth Registry, Danish National Patient Register, and Danish National Prescription Registry. Pregnancies with a gestational age of at least 12 weeks were included in the research; multiple pregnancies were not. One year of residence before and after pregnancy was necessary according to additional requirements. The term "montelukast exposure" refers to the length of time from three months prior to the conclusion of the first trimester until the prescription is redeemed. The pregnancy outcomes of women who had been exposed to montelukast were compared to groups whose asthma was managed with other drug profiles.

In Canada, pregnant women looking for information on the safety of montelukast participated in a prospective cohort study carried out [15]. After being diagnosed with asthma, the participants were divided into three groups: those taking additional medications for asthma, those who had not been exposed to any teratogenic chemicals, and the general population. The factors that matched were gestational age, maternal age, smoking, and alcohol consumption. Eight weeks following delivery to a year later, follow- up interviews was place. The information included the baby's features, health as a newborn, problems, medication use, birth information, and abnormalities. The study methodology used SPSS to perform a number of statistical analyses.

A research based in the United States was carried out [16] as part of the National Birth Defects Prevention research (NBDPS), a population-based case-control analysis spanning ten states from 1997 to 2007. Cases comprised live births with birth defects, stillbirths, and terminations; randomly chosen controls were matched by area. Medical data, with a focus on Congenital Heart Abnormalities (CHD), were evaluated by clinical specialists. One might classify CHDs as solitary or as having many abnormalities. Maternal demographic, medical, and prescription history information was obtained through structured phone interviews. Logistic regression was used to evaluate possible confounders and exclude specific instances from the analysis. The modification of effects was investigated for risk variables. Further analyses included examinations of specific forms of CHD, term births, pulmonary valve stenosis, and muscular VSD (**Table 1**).

Table 1: Summary of all the Studies Evaluated.

Title of Study	Study Design	Drugs Used	Study Findings (Summarized)
Safety of leukotriene receptor antagonists in pregnancy	Prospective Observational Study	Montelukast, Zafirlukast	The study concluded that LTRAs do not have teratogenic effects as significant as major teratogenic substances. It found that using LTRAs did not pose a substantial risk of adverse outcomes for both the mother and the fetus.
The safety of pranlukast and montelukast during the first trimester of pregnancy: A prospective, two-centered cohort study in Japan	Observational Retrospective Cohort Study	Montelukast, Pranlukast, Zafirlukast	The results revealed no noticeable trends in particular anomalies among those exposed to LTRAs, suggesting that these substances are unlikely to present a substantial teratogenic threat.
Fetal Exposure to Montelukast and Congenital Anomalies: A Population Based Study in Denmark	Cross-sectional Observational Epidemiological Study	Montelukast	Concluded that pregnant women with asthma who are prescribed asthma medications have increased chances of experiencing preterm delivery and maternal pregnancy-related complications. However, there was no significant rise in the likelihood of congenital abnormalities when the fetus was exposed to montelukast.
Montelukast use during pregnancy: a multicentre, prospective, comparative study of infant outcomes	Prospective Cohort Study	Montelukast, Other Asthma Drugs	The results exposure to montelukast during pregnancy did not result in higher rates of miscarriage, fetal deaths, or premature rupture of membranes.
Maternal asthma medication use during pregnancy and risk of congenital heart defects	Population-based Case-Control Study	Albuterol, Salmeterol, Ipratropium, Pirbuterol, Ephedrine, Epinephrine, Theophylline, Formoterol, Metaproterenol, Terbutaline, Fluticasone, Beclomethasone, Prednisone, Triamcinolon, Cromolyn, Budesonide, Montelukast, Zafirlukast, Prednisolone, Methylprednisolone, Nedocromil	Reported no statistically significant associations for most CHD categories, there were modestly increased risks observed in specific cases.

Discussion

1. Leukotriene antagonist receptor mechanism of action and uses:

Leukotrienes, lipid mediators essential to inflammation and immunological responses, are produced by 5-lipoxygenase from arachidonic acid [17]. By attaching to a particular lung receptor, they play a role in the pathophysiology of asthma. This has important biological ramifications, including bronchoconstriction, hyperresponsiveness of the bronchial smooth muscle, increased vascular permeability, and mucus production that causes tissue oedema and airflow obstruction[17]. Through the recruitment of inflammatory cells, particularly eosinophils, leukotrienes also have proinflammatory effects [18]. Furthermore, studies have shown that those who have asthma have higher amounts of leukotrienes, highlighting the importance of these molecules as biological mediators [19]. Remarkably, in vivo leukotriene synthesis has not been shown to be significantly reduced by oral or inhaled corticosteroids. Leukotrienes are a prime candidate for anti-asthma therapy because to their broad pharmacology in airway inflammation, which may provide additional benefits for individuals currently receiving the recommended dosage of inhaled corticosteroids [20]. Leukotriene receptor antagonists (LTRAs) proved to be the most successful of the several medication classes that surfaced, each of which had an effect on a distinct stage of the leukotriene biosynthesis process. Leukotriene receptors, namely the cysteinyl leukotriene receptors CysLT1 and CysLT2, are specifically blocked by LTRAs. Numerous cells, such as immune cells, smooth muscle cells, and airway epithelial cells, have these receptors. Their unique mechanism of action has a dual effect that includes anti-inflammatory and bronchodilatory actions [21]. LTRAs interfere with leukotrienes by competitively binding to the Leukotriene receptors, resulting in bronchodilation, reduced mucus secretion, and decreased inflammation in the airways [22].

The current asthma treatment recommendations advocate medium-dose maintenance Inhaled Corticosteroids (ICS) with formoterol as the best option for moderate-to-severe asthma, in accordance with the Global Initiative for Asthma (GINA) approach. When ICS-formoterol dose is appropriate, LTRAs are add-on therapy at GINA Steps 4 and 5. Alternatively, Steps 2 and 3 offer options for patients who prefer oral drugs or have trouble utilizing inhalers. LTRAs are mostly used to treat chronic asthma since studies have demonstrated that cysteinyl leukotrienes play a major role in the remodeling of the airways in those who have chronic asthma [23]. Because of their long half-lives and long-term efficacy in producing therapeutic effects, LTRAs are not appropriate as rescue drugs for acute asthmatic attacks [8]. Whereas Zafirlukast is recommended for prophylaxis and chronic treatment of asthma in children older than five years old and adults, Montelukast is approved for the prevention of exercise-induced bronchoconstriction, seasonal or perennial allergic rhinitis, and prophylaxis and chronic treatment of asthma in patients two years of age or older [8].

In general, LTRAs have a large safety margin and are generally tolerated. With Montelukast, there have been no notable drug interactions, and the medication has very few adult adverse effects—less than 2% of patients have any. Dyspepsia, headaches, and stomach discomfort are possible side effects. Viral infections and gastrointestinal disorders are common in children. In rare instances, neuropsychiatric conditions including anxiety, sleeplessness, and depression may also arise [8]. Although not shown beyond a reasonable doubt, there could be a link between montelukast usage and the development of Allergic Granulomatous Angiitis (Churg-Strauss syndrome), which means doctors should be cautious when treating individuals who show the typical symptoms. Montelukast and zafirlukast share a similar adverse effect profile. Furthermore, there have been few but severe occurrences of liver dysfunction as well as brief elevations in liver enzyme levels. As a result, it is not recommended for those with hepatic dysfunction, and routine liver enzyme testing is suggested. (Those who have a history of drug or component hypersensitivity should not use montrelukast or zafirlukast. Furthermore, because the formulation contains phenylalanine, individuals with phenylketonuria should not use montelucent [8].

While corticosteroids are generally the drug of choice for treating asthma initially, there are differences in how well steroid therapy works. Furthermore, taking more steroids might have serious negative effects. According to the demands of the patient, customized treatment plans are therefore necessary. Montelukast's efficacy has been shown in several investigations. The addition of montelukast to baseline ICS therapy resulted in a reduction in beta-agonist usage, an increase in overall quality of life, including increased activity levels, fewer nocturnal awakenings, and improved emotional well-being, as well as a clinically significant improvement in FEV1 (Forced Expiratory Volume in One Second [24]. These results highlight the amazing potential of montelukast as a useful asthma add-on medication.

Moreover, a lot of people have trouble sticking to their regular inhaled asthma treatments, which usually require using inhalers often. The oral LTRAs can be quite beneficial in these situations. This is especially helpful for young patients and older individuals who might have trouble using inhalers on their own. When opposed to inhalers, montelukast's simple once-daily oral dose is why parents of children with asthma prefer it. It also allays worries about possible long-term negative effects of corticosteroids, including as growth problems and anomalies in metabolism [8]. Compared to treatments requiring many daily doses, the ease of a once-day oral medicine greatly enhances long-term treatment compliance (**Table 2**).

2. LTRA utilisation across the trimesters

Leukotriene receptor antagonists (LTRAs) are anti-asthmatic drugs that are regularly recommended for pregnant women coping with asthma or allergic rhinitis that demands medical intervention. According to current asthma guidelines, managing LTRAs is necessary for effectively controlling severe asthma. The conventionally advised dosages and actual usage habits of medications vary greatly.

Table 2: Table of Leukotriene Receptor Antagonists (LTRAs).

LTRA	Common Brand Name	Indications	Dosage Forms	Additional Information
Montelukast	Singulair	Asthma, Allergic Rhinitis, Exercise induced bronchoconstriction	Tablets, Chewable Tablets, Granules	Preferred choice in pediatrics
Zafirlukast	Accolate	Asthma, Allergic Rhinitis	Tablets	Contraindicated in hepatic impairment
Pranlukast (Japan)	Onon	Asthma, Allergic Rhinitis	Tablets	Limited availability outside Japan

Placed a unique emphasis on the inclusion criteria, focusing solely on LTRA consumption by expectant mothers in the first trimester [25]. However, concentrated particularly on Montelukast, Hatakeyama. Both Montelukast and Zafirlukast were noted. Three months after the previous menstrual cycle began, the treatment plan was started, and it was followed for the duration of the first trimester.

The results differed from the earlier protocol, nevertheless, since they followed half of the women who were exposed to LTRAs during the first trimester and kept up regular use throughout the duration of their pregnancies [15]. The results indicate that ninety-six women used LTRAs during their pregnancies; of them, 72 used montelukast, 22 used zafirlukast, and 2 used both of them women obtained the recommended adult dosages of 10 mg of montelukast and 20 mg of zafirlukast together with other controller drugs. There was no discernible association between the prolonged usage of LTRAs and an increased risk of unfavorable maternal outcomes.

3. Applications of LTRA:

Leukotriene receptor antagonists, the first new class of anti-asthma therapies in three decades, are a game-changing addition to the anti-asthma arsenal, with a unique mix of anti-inflammatory and bronchodilator effects. Published clinical evidence on leukotriene receptor antagonists highlight their substantial efficacy in treating asthma over a wide spectrum of severity while making no statistical difference in fetal distress either as a standalone therapy strategy or in combination with inhaled corticosteroids Furthermore, these antagonists appear to be useful in controlling allergic rhinitis, which commonly coexists with asthma and urticaria in patients.

LTRAs are renowned for their safety and anti-asthmatic characteristics, which make them a useful intervention in asthma control during pregnancy. While these drugs are not the first choice of medication, they are widely recommended as a viable supplementary treatment for pregnant women who do not respond well to other asthma therapies or demonstrate resistance to other treatments prior to pregnancy, in order to avoid asthma exacerbations during pregnancy [15].

4 Alternative Medications

Leukotriene Receptor Antagonists (LTRAs) are frequently administered in combination with other controller medicines, including as short-acting beta anatagonists, corticosteroids, bronchodilators, and anti-inflammatory agents, as previously studied.

Three individual studies [12, 15, 25] describe the utilization of short-acting beta-agonists, inhaled and oral corticosteroids during pregnancy. Nonetheless, some studies have found that pregnant women take inhaled corticosteroids at a reduced rate due to the possible risk to the fetus. [26, 27]. The results showed that there was no significant difference in preterm births between continuous LTRA users and beta-agonist users.

On the contrary, demonstrate the usage of different bronchoconstrictors and anti-inflammatory medications among self-medicated pregnant women in order to assess the prevalence of fetal CHDs [16]. Albuterol was discovered to be the most commonly used bronchoconstrictor during pregnancy. Fluticasone, prednisone, and montelukast were the most common anti-inflammatory medicines used.

Except for cases of complete abnormal pulmonary venous return, no significant relationships were discovered between particular Congenital Heart Defects (CHDs) and the use of bronchodilators.

5. Congenital abnormalities and LTRA use

The World Health Organization defines congenital malformations as “structural or functional anomalies that occur during intrauterine life” [28]. This research shows that there is minimal evidence to indicate a direct relationship between fetal exposure to LTRAs such montelukast and congenital abnormalities. These investigations found no statistical significance between foetal montelukast exposure and congenital abnormalities; nonetheless, reduced birth weight was seen across the board [14, 15]. Low birth weights do not match the requirements for being classified as a congenital abnormality; hence they will not be examined further in this study.

Despite its low statistical power, the Danish population-based investigation found a statistically negligible increase in the incidence of congenital abnormalities among neonates exposed to montelukast as foetuses compared to those who were not exposed [14]. The most prevalent abnormalities under the umbrella term ‘congenital cardiac defects’ were identified in this study. These include Ventricular Septal Defects (VSD), Atrial Septal Defects (ASD), Atrioventricular Septal Defects (AVSD), and aortic coarctation [14]. Other congenital anomalies seen after montelukast exposure included cleft lip with or without cleft palate, anorectal atresia and stenosis, hypospadias, hydronephrosis, bladder exstrophy, and clubfoot. Each of these main congenital abnormalities was determined to be the most prevalent and induced by montelukast exposure throughout the fetal period [14].

Although LTRAs have not been demonstrated to cause serious congenital abnormalities [14], the mechanism of action for this family of medications may explain some of the concerns raised in this area. The majority of commercially available LTRAs target human cysteine LT1 (CysLT1) receptors, which are key mediators of airway smooth muscle activation [29]. CysLT1 receptors are most strongly expressed in peripheral blood leukocytes, although they are also less substantially expressed in the placenta [29]. Given the importance of the placenta in the proper development of the fetus [30], it is understandable that there is some worry about the use of LTRAs during pregnancy. However, whereas LTRAs may impact CysLT1 receptors within the placenta, this does not appear to raise the risk of major congenital malformations.

There is no direct evidence demonstrating a relationship between maternal LTRA usage and congenital abnormalities [14, 15], hence there is no literature tracking newborns’ development after fetal exposure to LTRAs. As a result, no inferences can be drawn about fetal exposure to LTRAs and their impact on newborn development. However, they found that the LTRA exposed group had a statistically negligible higher chance of acquiring a congenital cardiac defect [14]. Infants born with congenital heart problems are more likely to need corrective cardiac surgery, which has been linked to neurodevelopmental delays [31]. However, as congenital heart problems need corrective cardiac surgery to address this condition, no inferences about the relationship between fetal LTRA exposure and developmental delay can be made.

Although there is no proof linking the use of LTRAs by mothers to significant congenital abnormalities, the British National Formulary and the manufacturer both recommend using caution when

administering LTRAs during pregnancy [32]. As a result, medications are more frequently utilized to treat asthma in pregnant women. Inhaled beta-2 agonists and inhaled corticosteroids are the mainstays of these [33]. Like with any prescription prescribed for a pregnant woman, there is still prudence when it comes to administering these drugs during pregnancy [32, 34].

Maternal challenges in ltra use

Any decrease in these spirometric metrics should raise warning flags for pregnant asthmatic patients. Asthma and unfavorable pregnancy outcomes— preeclampsia [35- 37], placental abruption, placenta previa [35, 38], and obstetric hemorrhage [35, 38]—have a well-established association. Asthma has been regularly linked to increased incidence of cesarean delivery in several decades of study [36, 38]. Low birth weight and small-for- gestational-age newborns are among the many long-lasting and varied complications in the offspring associated with improperly treated maternal asthma [36, 39]. The risk of low birth weight increases with the severity of asthma [36]. As a result, it is critical to provide pregnant patients with asthma the right treatment measures since these patients' respiratory issues may cause challenges for both the mother and the fetus. These days, the most often used and safest drugs to take while pregnant are beta2-agonists, anticholinergics, glucocorticoids, theophylline, Leukotriene Receptor Antagonists (LTRAs), omalizumab, and Allergen Immunotherapy (AIT). Reduced asthma medication usage during pregnancy is associated with a twofold increased risk of wheezing episodes, particularly in areas with high nitrogen dioxide air pollution and in the summer months [40, 41].

For pregnant women with asthma, glucocorticoids, beta2-agonists, and omalizumab are viable substitutes for Leukotriene Receptor Antagonist (LTRA) medication. Since Inhaled Glucocorticoids (ICS) work locally in the airways, they have the added advantage of greatlylowering systemic pharmaceutical adverse effects while also effectively limiting the quantity and activity of inflammatory cells in the airway. Among the ICS used most frequently and safely during pregnancy is budesonide [42]. Beta2-agonists are often given via quantitative inhalation or atomization of the solution, and are safe for pregnant individuals with asthma at any dosage. Salbutamol, terbutaline, and pirbuterol are examples of Short-Acting Beta2-Agonists (SABA) that are used as pain relievers [42]. While omalizumab is used as a supplemental treatment for non-pregnant patients with chronic, moderate-to-severe asthma that is not well controlled with Inhaled Corticosteroids (ICS). A prospective analysis found that the incidence of significant congenital abnormalities linked to omalizumab treatment did not exceed that of cases reported in the overall asthma community. It does not appear to increase the incidence of Small- For-Gestational-Age (SGA) newborns or the risk of preterm over the levels seen in the general asthma population [43]. Omalizumab medication should not be started during pregnancy despite these encouraging results because of possible anaphylactic risks; if it is already under way, it may be continued in some circumstances [44].

Limitations of the study; 350 words

This systematic review identified a limited number of studies that matched the inclusion criteria. The small sample sizes in these studies may restrict the findings' generalizability. The included research used various study designs, such as prospective observational studies and retrospective cohort studies. The variety of study designs can induce unpredictability in the outcomes, making it difficult to draw solid conclusions. There is a risk of publication bias, as research with significant findings is more likely to be published than those with non-significant results. This bias might have an impact on the overall results of the review. The included studies examined LTRA usage during pregnancy; however, there may have been variations in the specific LTRA drugs used, doses, and length of therapy between researches. These discrepancies may have an influence on the findings and comparisons made between the researches. The majority of the research cited did not offer long-term follow-up data on babies exposed to LTRAs during pregnancy. Thus, the long- term consequences of LTRA exposure on baby development and health outcomes are unknown. Confounding variables in the trials, including as maternal asthma severity, concurrent medication usage, and other maternal health issues, may not have been sufficiently accounted for. These factors may impact the outcomes and cause bias. The research relied on self-reporting and medical records, which may have introduced bias into the data. The accuracy and completeness of the data obtained may differ between researches, influencing the validity of the conclusions. The lack of RCTs explicitly testing LTRA usage in pregnancy and congenital abnormalities reduces the availability of high-quality evidence. RCTs are regarded the gold standard for demonstrating causal links. These studies were confined to those written in English, which may have introduced linguistic bias. Relevant papers published in other languages may have been overlooked, thereby compromising the review's comprehensiveness. analysis, and reporting of findings.

Conclusion

We carefully considered and evaluated each study before selecting and analyzing five of them for this publication. In this work, we investigate the safety of LTRA usage during pregnancy and its potential correlation with fetal congenital abnormalities. LTRAs do not exhibit teratogenic qualities of a considerable size that are equivalent to those of major teratogenic drugs. The findings suggest that there was no appreciable risk of adverse effects for the mother or the fetus while using LTRAs. According to research there was no discernible correlation found between exposure to LTRAs, such as pranlukast, and a higher risk of serious congenital abnormalities during the first trimester of pregnancy. The results suggested that there is little chance of a major teratogenic risk associated with LTRAs and did not reveal any patterns of particular abnormalities in the group exposed to LTRAs.

This study also provides reassurance on the safety of LTRAs, such as pranlukast, in the treatment of pregnant women's asthma. According to expecting mothers who have asthma and are taken asthma drugs are more likely to experience difficulties linked to their pregnancy, including premature birth. However, there was no discernible increase in the risk of congenital defects after montelukast exposure during pregnancy. The results of demonstrate that the observed rate of congenital abnormalities (1-3%) is comparable to the general population and that exposure to montelukast in gestation did not raise the risk of miscarriage, fetal mortality, or preterm membrane rupture.

Nonetheless, it was noted that the newborns in both asthmatic woman groups were smaller, which may have been related to how severe their asthma was. For the majority of CHD categories found no statistically significant relationships; however, in few circumstances, slightly elevated risks were noted. To make progress in this area and ascertain the safety of using LTRAs during pregnancy,

post marketing surveillance, carried out by pharmaceutical firms and regulatory bodies, must be implemented. This can offer actual data on unfavorable outcomes linked to LTRA usage in expectant mothers. We must look at the biological processes that underlie LTRAs and how they could affect fetal development in order to understand their safety profile during pregnancy. Further research on the possible hazards to the growing fetus might be obtained by doing pharmacokinetic studies to ascertain the placental transfer and fetal exposure to LTRAs.

References

1. Peebles RS & Aronica MA (2019) Proinflammatory Pathways in the Pathogenesis of Asthma. Clin Chest Med; 40(1): 29-50.
2. Leukotriene Receptor Antagonists [Internet]. PubMed. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
3. Rådmark O, Werz O, Steinhilber D, Samuelsson B (2015) 5-Lipoxygenase, A Key Enzyme for Leukotriene Biosynthesis in Health and Disease. Biochim Biophys Acta; 1851(4):331-339.
4. Jo-Watanabe A, Okuno T, Yokomizo T (2019) The Role of Leukotrienes as Potential Therapeutic Targets in Allergic Disorders. Int J Mol Sci; 20 (14):3580.
5. Gelfand EW (2017) Importance of the Leukotriene B4-BLT1 and LTB4-BLT2 Pathways in Asthma. Semin Immunol; 33:44-51.
6. Xiong Y, Cui X, Li W, Lv J, Du L, et al. (2019) BLT 1 Signaling in Epithelial Cells Mediates Allergic Sensitization Via Promotion of IL-33 Production. Allergy; 74(3):495-5066.
7. Elieh Ali Komi D, Bjermer L (2019) Mast Cell-Mediated Orchestration of the Immune Responses in Human Allergic Asthma: Current Insights. Clin Rev Allergy Immunol; 56(2):234-247.
8. Choi J, Azmat CE. Leukotriene Receptor Antagonists
9. Holgate ST, Church MK, Broide DH. Allergy. Edinburgh: Elsevier Saunders, Cop; 2012.
10. Erdem SB, Nacaroglu HT, Karkiner CS, Gunay I, Can D (2015) Side Effects of Leukotriene Receptor Antagonists in Asthmatic Children. Iranian J Pediatr; 25(5).
11. Cusack RP, Whetstone CE, Gauvreau GM (2023) Use of Asthma Medication during Gestation and Risk of Specific Congenital Anomalies. Immunol Allergy Clin North Am; 43(1):169-185.
12. Bakhireva LN, Jones KL, Schatz M, Klonoff-Cohen HS, Johnson D, et al. (2007) Safety of Leukotriene Receptor Antagonists in Pregnancy. J Allergy Clin Immunol; 119(3):618–625.
13. Wang J, Zhou Y, Zhang H, Hu L, Liu J, et al. (2023) Pathogenesis of Allergic Diseases and Implications for Therapeutic Interventions. Signal Transduct Target Ther ;8(1):138
14. Cavero-Carbonell C, Vinkel-Hansen A, Rabanque-Hernández MJ, Martos C, Garne E (2017) Fetal Exposure to Montelukast and Congenital Anomalies: A Population Based Study in Denmark. Birth Defects Res; 109(6):452-459.
15. Sarkar M, Koren G, Kalra S, Ying A, Smorlesi C, et al. (2009). Montelukast Use during Pregnancy: A Multicentre, Prospective, Comparative Study of Infant Outcomes. Eur J Clin Pharmacol ;65(12):1259-1264.
16. Van Zutphen AR, Bell EM, Browne ML, Lin S, Lin AE, Druschel CM & National Birth Defects Prevention Study (2015). Maternal Asthma Medication Use during Pregnancy and Risk of Congenital Heart Defects. Birth Defects Res a Clin Mol Teratol; 103(11):951-961.
17. Samuelsson B (1983) Leukotrienes: Mediators of Immediate Hypersensitivity Reactions And Inflammation. Science; 220(4597): 568-575.
18. Busse WW (1998) Leukotrienes and Inflammation. Am J Respir Crit Care Med; 157(6):S210-S213.
19. Wardlaw AJ, Hay H, Cromwell O, Collins JV, Kay AB.(1989) Leukotrienes, LTC4 and LTB4, in Bronchoalveolar Lavage in Bronchial Asthma and Other Respiratory Diseases. J Allergy Clin Immunol; 84(1):19-26.
20. Dworski R, Fitzgerald GA, Oates JA, Sheller JR (1994) Effect of Oral Prednisone on Airway Inflammatory Mediators in Atopic Asthma. Am J Respir Crit Care Med; 149(4):953-959.
21. Dempsey OJ (2000) Leukotriene Receptor Antagonist Therapy. Postgrad Med J; 76(902):767-773.
22. 2022 GINA Main Report - Global Initiative for Asthma. (2023). Retrieved from https://ginasthma.org/gina-reports/
23. Hallstrand TS, Henderson Jr WR (2010) An Update on the Role of Leukotrienes in Asthma. Curr Opin Allergy Clin Immunol; 10(1):60-66.
24. Vaquerizo MJ, Casan P, Castillo J, Perpina M, Sanchis J, et al.(2003)Effect of Montelukast Added to Inhaled Budesonide on Control of Mild to Moderate Asthma. Thorax; 58(3):204-210.
25. Hatakeyama S, Goto M, Yamamoto A, Ogura J, Watanabe N, et al.(2022) The Safety of Pranlukast and Montelukast during the First Trimester of Pregnancy: A Prospective, Two-Centered Cohort Study in Japan. Congenit Anom; 62(4):161-168.
26. Enriquez R, Wu P, Griffin MR, Gebretsadik T, Shintani A, et al.(2006) Cessation of Asthma Medication in Early Pregnancy. Am J Obstet Gynecol; 195(1):149-153.
27. Schatz M, Leibman C (2005) Inhaled Corticosteroid Use and Outcomes in Pregnancy. Ann Allergy Asthma Immunol; 95(3):234-238.
28. WHO. (2023). Congenital Disorders. Retrieved from https://www.who.int/ news-room/fact-sheets/detail/birth-defects
29. Vedanthan PK, Nelson HS, Agashe SN, Mahesh PA, Katial R, et al. (2014) Textbook of Allergy for the Clinician. CRC Press, Taylor & Francis Group.
30. Burton GJ, Fowden AL (2015) The Placenta: A Multifaceted, Transient Organ. Philos Trans R Soc Lond B Biol Sci; 370(1663):20140066.
31. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, et al. (2015) Neurodevelopmental Outcomes After Cardiac Surgery In Infancy. Pediatrics; 135(5):816-825.
32. Joint Formulary Committee (2012). British national formulary (Vol. 64). Pharmaceutical Press.
33. Charlton RA, Pierini A, Klungsøyr K, Neville AJ, Jordan S, et al. (2016). Asthma Medication Prescribing Before, During and After Pregnancy: A Study in Seven European Regions. BMJ Open; 6(1):e009237
34. El Shamy T, Tamizian O (2018) Principles of Prescribing In Pregnancy. Obstetrics, Gynaecology & Reproductive Medicine; 28(5): 136-140.
35. Mendola P, Laughon SK, Männistö TI, Leishear K, Reddy UM, et al. (2013) Obstetric Complications among Us Women with Asthma. Am J Obstet Gynecol; 208(2):127.e1–127.e8.
36. Rejnö G, Lundholm C, Gong T, Larsson K, Saltvedt S, et al. (2014) Asthma During Pregnancy In A Population-Based Study-Pregnancy Complications and Adverse Perinatal Outcomes. PLoS One; 9(8): e104755.
37. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, et al. (2011) A Meta-Analysis of Adverse Perinatal Outcomes in Women with Asthma. BJOG; 118(11): 1314-1323.
38. Wang G, Murphy VE, Namazy J, Powell H, Schatz M, et al. (2014) The Risk of Maternal and Placental Complications in Pregnant Women with Asthma: A Systematic Review and Meta-Analysis. J Matern Fetal Neonatal Med; 27(9): 934-942.
39. Mendola P, Männistö TI, Leishear K, Reddy UM, Chen Z, Laughon SK (2014) Neonatal Health of Infants Born to Mothers with Asthma. J Allergy Clin Immunol; 133 (1): 85-90.
40. Gent JF, Kezik JM, Hill ME, McKay LA, Holford TR, et al. (2015). Asthma Medication Use During Pregnancy, Wheeze and Estimated Exposure to Ambient Nitrogen Dioxide. Eur Respir J; 45(2): 538-540.
41. Bonham CA, Patterson KC, Strek ME (2018) Asthma Outcomes and Management during Pregnancy. Chest; 153(2): 515-527.
42. Wang H, Li N, Huang H (2020) Asthma in Pregnancy: Pathophysiology, Diagnosis, Whole-Course Management, and Medication Safety. Can Respir J; 2020.

43. Namazy J, Cabana MD, Scheuerle AE, Thorp Jr JM, Chen H, et al. (2015) The Xolair Pregnancy Registry (EXPECT): The Safety of Omalizumab Use during Pregnancy. J Allergy Clin Immunol; 135(2): 407-412.

44. Kelly W, Massoumi A, Lazarus A (2015) Asthma in Pregnancy: Physiology, Diagnosis, and Management. Postgrad Med; 127(4): 349-358.