Complex interplays: Asthma management and maternal-fetal outcomes in pregnancy (Review)

VASILIKI EPAMEINONDAS GEORGAKOPOULOU[1], CHRYSOULA TASKOU[2], DEMETRIOS A. SPANDIDOS[3] and ATHINA DIAMANTI[2]

[1]Department of Pathophysiology, Laiko General Hospital, Medical School of National and Kapodistrian University of Athens, 11527 Athens, Greece; [2]Department of Midwifery, Faculty of Health and Caring Sciences, University of West Attica, 12243 Athens, Greece; [3]Laboratory of Clinical Virology, School of Medicine, University of Crete, 71003 Heraklion, Greece

Received June 15, 2024; Accepted September 18, 2024

DOI: 10.3892/etm.2024.12744

Abstract. Asthma, a common chronic respiratory condition, poses unique challenges in pregnancy, impacting both maternal and fetal health. Of note, 8-13% of pregnant women suffer from asthma, a condition that can worsen, stabilize, or improve during pregnancy. These fluctuations necessitate a nuanced management strategy to ensure the health of both the mother and fetus. Adverse outcomes, such as preeclampsia, gestational diabetes and increased cesarean delivery rates are associated with poorly controlled asthma. From a fetal perspective, the risks include preterm birth and a low birth weight. Physiological changes in pregnancy, such as an increased tidal volume and altered drug metabolism due to increased blood volume, complicate the management of asthma. The safety of asthma medications during pregnancy remains a significant concern, with ongoing research into their teratogenic effects. Recent advancements in treatment include the development of biologics and the increased use of personalized medicine, integrating pharmacogenomics and immunological profiling to tailor treatments to individual needs. Digital health tools have also emerged, enabling improved patient monitoring and management. The present review highlights the complex interplay between asthma management and pregnancy outcomes, advocating for comprehensive care approaches that consider the dynamic physiological changes during pregnancy. It underscores the need for ongoing research into the safety of medication and innovative therapeutic strategies to improve health outcomes for pregnant women with asthma and their babies.

Correspondence to: Dr Vasiliki Epameinondas Georgakopoulou, Department of Pathophysiology, Laiko General Hospital, Medical School of National and Kapodistrian University of Athens, 17 Agiou Thoma Street, 11527 Athens, Greece
E-mail: vaso_georgakopoulou@hotmail.com

Key words: asthma in pregnancy, maternal-fetal health, medication safety, physiological changes, treatment advances

Contents

1. Introduction

Asthma is a common chronic respiratory condition marked by inflammation of the airways, the reversible obstruction of airflow and an increased sensitivity of the bronchi (1). This disease affects millions of individuals globally, markedly affecting their quality of life (QoL) and placing a substantial burden on healthcare systems. According to the Centers for Disease Control and Prevention (CDC), asthma affects ~25 million Americans, which translates to ~1 in 13 individuals (2). Globally, the prevalence of asthma varies; however, it remains a critical public health challenge (3).

In pregnant women, the prevalence of asthma is noteworthy, affecting 8-13% of pregnancies (4). Pregnancy can alter the course of asthma, with approximately one-third of pregnant women experiencing more severe symptoms, one-third remaining stable and one-third observing an improvement in their asthma condition (5). This variability introduces significant challenges in the management of asthma during pregnancy, necessitating a nuanced approach to treatment that considers both maternal and fetal health. Multiple factors compound the management of asthma in pregnancy, increasing both maternal and fetal risks (6,7). These risks underscore the importance of optimal asthma management during pregnancy.

The physiological changes that occur during pregnancy, such as the increased tidal volume and decreased functional residual capacity, can complicate the standard asthma treatment protocols (8). Furthermore, the safety of various asthma medications during pregnancy continues to be a pivotal concern, with ongoing research focusing on understanding the teratogenic effects of traditional and newer asthma medications (6).

The present review discusses the novel challenges in the management of asthma during pregnancy, particularly focusing on the physiological, pharmacological and therapeutic complexities introduced by pregnancy. The present review also discusses recent advancements in treatment strategies that have emerged in response to these challenges. These achievements include the development and increased use of biologics in pregnancy, innovations in personalized medicine approaches, and the integration of digital health tools into patient monitoring and management strategies.

2. Physiological changes that occur during pregnancy

Physiological changes occurring in pregnancy. Pregnancy induces notable physiological changes that can affect almost every organ system, including the respiratory system. These changes can exacerbate asthma or influence the effectiveness and pharmacokinetics of medications for asthma management.

Respiratory and cardiovascular changes. During pregnancy, several physiological changes occur that can complicate asthma management. Increased progesterone levels stimulate the respiratory center in the medulla, resulting in a 40% increase in tidal volume and a 50% increase in minute ventilation, while the respiratory rate remains stable (9). These changes are essential to meet the heightened oxygen demands of both the mother and fetus. However, they also reduce arterial partial pressure of carbon dioxide and elevate respiratory alkalosis, potentially exacerbating airway hyperresponsiveness and altering responses to asthma medications (10).

The cardiovascular system also undergoes significant adaptations during pregnancy, with the blood volume increasing by 30-50% to ensure adequate placental perfusion and meet the metabolic needs of the mother and fetus. This hemodilution reduces drug concentrations in the bloodstream, and combined with the enhanced renal blood flow, it can lead to the more rapid clearance of asthma medications, such as bronchodilators and corticosteroids. Consequently, standard doses may not achieve therapeutic levels, necessitating careful and potentially frequent adjustments to dosing regimens (11).

Immunologic and mechanical changes. Immunologically, pregnancy induces a shift from a T-helper 1 (ThH1) to a T-helper-2 (ThH2) dominance to prevent fetal rejection. However, this ThH2-dominant response also increases antibody production and the likelihood of developing allergic reactions, common triggers for asthma exacerbations. For pregnant women with asthma, this shift can increase the frequency and severity of symptoms, particularly if their asthma is allergy-driven. Therefore, healthcare providers need to reassess treatment plans to accommodate these immunological changes, potentially requiring more aggressive or different therapeutic approaches (12).

Mechanically, the growing uterus elevates the diaphragm, reducing the space within the thoracic cavity and decreasing total lung capacity. This elevation primarily affects the residual volume, the amount of air remaining in the lungs following a forced exhalation. Although vital capacity remains stable, the reduced lung space can cause a sensation of labored breathing. Asthma sufferers may experience increased shortness of breath, necessitating adjustments in management strategies, such as the more frequent use of inhaled bronchodilators or changes in the timing of medication administration (13).

3. Medication safety and treatment strategies

Medication safety. Ensuring the safety of asthma medications during pregnancy is critical because of the potential risks to both the mother and the fetus. Recent research has provided considerable insight into the safety profiles of various asthma medications when used during pregnancy.

Inhaled corticosteroids (ICS) and oral corticosteroids. ICS are the cornerstone of asthma management and have been extensively studied for their safety during pregnancy. Oral corticosteroids are used to treat severe asthma attacks (14).

The study by Schatz *et al* (15) assessed the safety of various asthma and allergy medications during pregnancy among 824 women with asthma and 678 controls without asthma. Medications analyzed included β-agonists and corticosteroids. The primary outcomes investigated were major congenital malformations, preeclampsia, preterm birth, a low birth weight and infants who were small for their gestational age. Their study found no significant associations between the use of these medications and an increased risk of major congenital malformations or other adverse perinatal outcomes, except for oral corticosteroids, which were associated with an increased risk of preeclampsia [odds ratio (OR), 2.0] (15). Furthermore, a dose-response association was noted with corticosteroid exposure and adverse outcomes, such as preeclampsia, preterm birth and low birth weight. However, their study highlighted that the risks associated with severe asthma potentially outweigh the risks posed by medications, supporting the continued use of oral corticosteroids when necessary, during pregnancy (15).

The study by Martel *et al* (16) examined the potential risks associated with the use of ICS during pregnancy, specifically as regards pregnancy-induced hypertension (PIH) and pre-eclampsia among asthmatic women. Utilizing data from three Quebec health databases, their study analyzed 3,505 women with asthma across 4,593 pregnancies (16). The findings of their study indicated no significant association between the use of ICS and an increased risk of developing PIH or pre-eclampsia. However, the use of oral corticosteroids was associated with a significant increase in the risk of developing PIH, with a trend toward an increased risk of pre-eclampsia (16).

Another study by Bracken *et al* (17) investigated the impact of asthma and its treatment on pregnancy outcomes, specifically focusing on preterm delivery and intrauterine growth restriction among 2,205 pregnant women, including 873 women with a history of asthma. Their study found that while asthma severity and symptoms did not significantly affect the risk of preterm delivery, the use of certain medications, particularly oral corticosteroids, was associated with an increased risk of preterm delivery (17). Women using oral corticosteroids experienced reductions in gestational length by ~2.22 weeks (17).

In addition, the study by Blais *et al* (18) investigated the risk of congenital malformations associated with the use of ICS during the first trimester of pregnancy among women with

asthma. The cohort of their study comprised 4,561 pregnancies from women who delivered between 1990 and 2000. Their study specifically evaluated the association between varying doses of ICS and the incidence of congenital malformations (18). The key findings were that 9.2% of the pregnancies resulted in congenital malformations, with 6.1% being classified as major malformations. Of note, ~40% of the women used ICS during the first trimester, with only 5.3% using doses >500 mg/day. The adjusted OR for all congenital malformations with ICS use was 0.77 for doses between 1-500 mg/day, 0.41 for doses between 501-1,000 mg/day, and 1.00 for doses >1,000 mg/day. For major malformations, the adjusted ORs were 0.90, 0.56 and 1.67 for the respective dose categories, respectively (18). Their study concluded that the use of ICS during the first trimester was not associated with an increased risk of congenital malformations, even at higher doses. These results support the safety of ICS treatment during pregnancy, aligning with recommendations to maintain asthma control to prevent adverse maternal and fetal outcomes (18).

The study by Bakhireva *et al* (19) evaluated the effects of asthma medications, specifically ICS and oral corticosteroids on fetal growth during pregnancy. The study included 654 infants born to mothers with asthma and 303 infants born to mothers without asthma as controls. The key findings indicated that the use of systemic corticosteroids was associated with a decrease in mean birth weight, with infants born to these mothers weighing ~200 g less compared to those exposed only to β-agonists or no asthma medications. However, no significant differences were found in the incidence of small for gestational age infants among the different medication groups, including ICS users (19). That study also noted that mean birth length and head circumference did not significantly differ among the groups. That study concluded that while systemic corticosteroids had a minimal effect on birth weight, the use of ICS did not impair fetal growth (19).

Furthermore, the study by Otsuka *et al* (20) investigated the safety and efficacy of ICS for asthma management in pregnant women. That retrospective study reviewed the records of 592 asthmatic pregnant women who delivered at a Japanese hospital between 1987 and 2003. The key findings of that study indicated that the use of ICS increased significantly over the study period, from 0% in 1987-1989 to 83.3% in 2000-2003. The incidence of intrapartum asthma attacks markedly decreased in women treated with ICS, with no attacks reported from 2000 to 2003, contrasting with a 1.38% incidence from 1995 to 1999 among those treated with inhaled β-agonists alone (20). Perinatal abnormalities were more common among untreated women and those with severe asthma. The incidence of these abnormalities decreased significantly from 59.6% before 1995 to 26.2% after 1995 in the treated group, particularly among those using ICS. Comparisons revealed no significant differences in perinatal outcomes between women treated with ICSs and those treated with other asthma medications, apart from a slightly higher incidence of premature rupture of membranes in the ICS group, which still fell within the expected range. Their study concluded that ICS are safe and effective for preventing asthma attacks during pregnancy and reducing perinatal abnormalities (20).

Rahimi *et al* (21) performed a large meta-analysis which demonstrated that ICS do not elevate the risk of significant malformations, preterm delivery, low birth weight, or pregnancy-induced hypertension. Notably, they enhance symptom management and are beneficial in treating asthma, rendering them safe for use during pregnancy (21). These findings are critical as they support the continued use of ICS in pregnant women with asthma to maintain asthma control and reduce exacerbations.

β-agonists. As regards the use of β-agonists during pregnancy, studies have extensively evaluated the safety of short-acting β-agonists (SABAs) and long-acting β-agonists (LABAs) to ensure they do not pose significant risks to the developing fetus (22,23). Research has consistently shown that these medications, crucial for asthma management, are generally safe for use during pregnancy and are not associated with major teratogenic risks (22,23). This means that the use of SABAs and LABAs does not increase the likelihood of congenital anomalies or developmental issues in the fetus. Therefore, they serve as an effective and safe component of an asthma treatment regimen during pregnancy, guaranteeing optimal asthma control for the mother, without jeopardizing the health of the fetus. This safety profile supports the continued use of these medications by pregnant women who require asthma management, aligning with current medical guidelines and practices (22,23).

The study by Lao and Huengsburg (24) retrospectively analyzed the outcomes of pregnancy and labor in 87 asthmatic mothers compared to a matched group of non-asthmatic controls. The primary focus was on evaluating the safety and impact of bronchodilator therapy, including the use of β-agonists, during pregnancy. The results of their study indicated that bronchodilator therapy in asthmatic mothers was not associated with an increased incidence of adverse outcomes, such as preterm delivery, post-term delivery, low birth weight, instrumental deliveries, postpartum hemorrhage, or perinatal complications. However, there was a higher incidence of caesarean sections in asthmatic mothers, particularly among those receiving bronchodilator treatment. This was possibly linked to a slightly higher rate of labor induction in these patients (24). Additionally, that study found that well-controlled asthma during pregnancy, even with the use of bronchodilator therapy, did not significantly differ from normal controls in terms of overall pregnancy outcomes. The presence or history of asthma, when managed effectively, did not adversely influence the outcome of labor, with factors such as labor induction and epidural analgesia playing a more significant role. The findings suggest that with appropriate management, including the use of bronchodilators, the risks associated with asthma in pregnancy can be minimized, supporting the safety of β-agonists during this period (24).

The study by Lin *et al* (25) explored the association between the maternal use of asthma medications during the periconceptional period and the risk of gastroschisis, a congenital abdominal wall defect. That case-control study used data from the National Birth Defects Prevention Study, covering births from 1997 to 2002, including 381 cases of gastroschisis and 4,121 controls without malformations (25). That study found that the maternal use of bronchodilators during the periconceptional period was associated with an increased risk of gastroschisis [adjusted OR, 2.06; 95% confidence interval (CI),

1.19-3.59]. The risk was particularly elevated for women who used multiple bronchodilators concurrently during this period, suggesting a potential dose-response association (25). The findings of that study indicate a potential association between bronchodilator use and an increased risk of gastroschisis, although that study could not definitively separate the effects of medication from the effects of asthma severity. The authors of that study highlighted the need for further research to determine whether the increased risk is due to the medication itself or the underlying uncontrolled asthma (25). That study underscored the importance of carefully managing asthma during pregnancy, while considering the potential risks and benefits of asthma medications (25).

Another study by Clifton *et al* (26) examined the effects of inhaled glucocorticoids and combination therapy with LABAs on placental function and neonatal birthweight in pregnancies complicated by asthma. Their study included 41 pregnant women with asthma and a control group of 20 non-asthmatic women. The asthmatic group was further divided based on their medication: Budesonide alone, fluticasone propionate alone, and a combination of fluticasone propionate with the LABA salmeterol (26). The key findings were that the use of inhaled budesonide was associated with an increased placental 11β-HSD-2 activity, an enzyme critical for protecting the fetus from excess maternal glucocorticoids. This group also exhibited normal birthweight outcomes, suggesting that inhaled budesonide does not adversely affect fetal growth. By contrast, the combination therapy group (fluticasone/salmeterol) exhibited reduced birthweight centiles, although without significant changes in placental 11β-HSD-2 activity (26). This suggests a potential impact of LABAs on fetal growth, although the small sample size necessitates further investigation. The study by Clifton *et al* (26) concluded that while ICS alone appeared safe and beneficial in managing asthma during pregnancy, the combination with LABAs may require closer monitoring.

Leukotriene receptor antagonists. Numerous studies have examined the safety and effects of leukotriene-receptor antagonists (LTRAs), such as montelukast and pranlukast, on both the mother and the baby during pregnancy.

For example, in 2007, Bakhireva *et al* (27) assessed the safety of LTRAs by comparing perinatal outcomes among women who used LTRAs, those who used short-acting β-agonists and women without asthma. Their findings demonstrated that LTRAs were not associated with increased risks of adverse outcomes, such as pregnancy loss, gestational diabetes, preeclampsia, low maternal weight gain, preterm delivery, low Apgar scores, or reduced birth length and head circumference. They noted a slight decrease in birth weight among infants born to LTRA users, likely due to the severity of the asthma of the mother (27).

Sarkar *et al* (28) in 2009 also examined the use of montelukast during pregnancy in a multicenter, prospective, comparative study. Their research involved 180 montelukast-exposed pregnancies, resulting in 160 live births. Their study noted lower birth weights and shorter gestational ages for montelukast-exposed infants but found no significant increase in major malformations (28).

Subsequently, Koren *et al* (29) in 2010 observed statistically smaller babies and shorter gestational ages in 180 cases of pregnant women exposed to montelukast compared to groups not exposed to teratogens. However, these differences were not significant when compared to a disease-matched group. It was found that ~25% of the newborns experienced fetal distress, with only one reported case of major malformation among the 143 infants exposed during organogenesis (29). The conclusion of that study was that montelukast does not significantly increase the risk of major malformations in the general population beyond the baseline risk (29).

In 2017 Cavero-Carbonell *et al* (30) conducted a Danish study analyzing registry data to evaluate pregnancy outcomes related to montelukast exposure. In montelukast-exposed pregnancies, that study included 754,300 singleton pregnancies and found increased risks of preterm birth and maternal complications, such as preeclampsia and gestational diabetes. However, that study found no significant increase in major congenital anomalies, indicating that the severity of the underlying maternal asthma may have a greater influence on montelukast-related risks than the medication itself (30).

Subsequently, in 2022, Hatakeyama *et al* (31) focused on montelukast and pranlukast, analyzing outcomes from 231 pregnant women exposed to these medications during the first trimester compared to control groups. Their study reported a 1.9% incidence of major congenital anomalies, with no significant increase in risk indicated by multivariable logistic regression analysis. The results of that study suggested that montelukast and pranlukast do not elevate the risk of major congenital anomalies, reinforcing their safety for asthma management during pregnancy (31).

Iin 2023, Tsai *et al* (32) utilized Taiwan's National Health Insurance Research Database to study the association between LTRA use during pregnancy and the occurrence of neuropsychiatric events (NEs) in offspring. That study, which covered 576,157 mother-offspring pairs, including 1,995 children exposed to LTRAs, found no significant associations between prenatal LTRA exposure and the development of attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), or Tourette syndrome in children (32). The findingsof that study indicate that LTRAs do not increase the risk of NEs in offspring, providing reassurance for their use in pregnant women with asthma or allergic rhinitis (32).

Overall, these studies suggest that while LTRAs, such as montelukast and pranlukast may be associated with certain risks such as a lower birth weight and a shorter gestational age, they do not significantly increase the risk of major birth defects and are generally safe for managing asthma during pregnancy. However, the underlying maternal asthma may contribute to the observed risks, and further studies are recommended to clarify these associations. They can be a valuable part of a comprehensive asthma management plan, particularly for women who do not respond well to other types of medications. Further research is required on these associations to guarantee the safety and effectiveness of LTRAs in pregnant populations.

Biologics. Researchers have evaluated newer biological therapies for pregnant populations, such as omalizumab, which targets IgE antibodies. Limited studies suggest that omalizumab is safe during pregnancy (as mentioned below). The 'Xolair Pregnancy Registry (EXPECT)' report is a summary of a study that investigated the safety of omalizumab use

during pregnancy (33). That study focused on the outcomes for the mother, the pregnancy and the baby, including the number of birth defects. That study included 191 pregnant women exposed to omalizumab, with data collection occurring at various stages from enrollment to 18 months post-delivery. The outcomes for 169 pregnancies indicated 156 live births, 11 spontaneous abortions, one stillbirth and one elective termination. Among the live births, 14.5% of infants were born prematurely, 10.9% were small for their gestational age, and 3.2% had low birth weights. There were 20 infants with confirmed congenital anomalies, with 7 infants having major defects and no unusual pattern of anomalies (33). Overall, the results of that study suggest that omalizumab exposure during pregnancy does not significantly deviate from expected congenital anomaly rates in the general population or among asthma sufferers, indicating no additional risk from the drug during pregnancy (33).

The study by Namazy *et al* (34) in 2020 compared the pregnancy outcomes of women treated with omalizumab and a disease-matched cohort not receiving omalizumab. Their study monitored 250 pregnant women with asthma who received omalizumab treatment and compared their outcomes with those of 1,153 pregnant women with moderate-to-severe asthma who did not receive the treatment. The results of their study revealed that the prevalence of major congenital anomalies was 8.1% in the omalizumab-exposed group and 8.9% in the comparator group, indicating no significant difference in the risk of congenital anomalies between the two groups. Furthermore, the rates of live births and premature births were similar between the two groups, suggesting that the use of omalizumab during pregnancy does not increase the risk of these outcomes compared to a similar population not treated with the drug (34).

Gemicioğlu *et al* (35) in 2021 examined the safety of omalizumab treatment in pregnant patients with asthma and found it to be safe for both mothers and their infants. The researchers observed improvements in asthma control measures during and after pregnancy compared to before treatment initiation, after analyzing data from 20 pregnant women treated with omalizumab. While 36.4% of the women experienced asthma exacerbations during pregnancy, there were no congenital anomalies among the 23 infants born, although there were instances of low birth weight and premature births. That study concluded that omalizumab does not significantly increase risks for pregnant patients or their offspring (35).

In 2022, Shakuntulla and Chiarella (36) provided an extensive analysis of the safety of using biologics in pregnant women with atopic diseases. The focus of their study was on seven FDA-approved biologics: Omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab and tralokinumab. The data compiled from various sources, primarily case reports and observational studies, involved a total of 313 pregnancies (36). Their study found no significant evidence that these biologics negatively affect pregnancy outcomes, including preterm delivery, low birth weight, or congenital malformations. This suggests that the underlying atopic condition worsening is more likely to affect pregnancy viability than the biologics themselves. However, the authors of that study call for more extensive prospective studies and registries to better assess the long-term safety and effects of biologics on maternal and fetal health, acknowledging the limitations of the current data due to the small sample sizes and lack of controlled studies (36).

Collectively, the data remain relatively limited, and biologics are typically reserved for patients with severe asthma who do not respond to other treatments.

Innovative therapeutic approaches. In addition to the ongoing evaluation of medication safety, there have been significant advancements in personalized care plans, biologic treatments for severe asthma, the use of inhaled corticosteroids and enhanced monitoring techniques during pregnancy (37).

Integrated care approaches. Healthcare professionals, including obstetricians, pulmonologists, allergists, and primary care providers, have recognized the efficacy of multidisciplinary care models in managing asthma during pregnancy. Research has shown that these integrated care approaches significantly improve the outcomes of pregnant women with asthma by providing comprehensive and cohesive care. The key components of such models typically include customized asthma action plans tailored to meet the unique needs of each patient. These plans outline detailed strategies for managing symptoms and provide clear instructions on how to adjust medications safely during pregnancy. These approaches require regular monitoring to promptly identify and address any changes in the condition of the patient or response to treatment. This proactive surveillance helps mitigate the risks associated with asthma exacerbations during pregnancy, which can pose significant health risks to both the mother and fetus. Adjustments to therapy are based on a thorough assessment of the current condition of the patient, considering factors, such as gestational age and any other complications or comorbidities (38).

Utilizing telemedicine and digital health tools. The advent of telemedicine and digital health tools has transformed the management of chronic diseases, including asthma during pregnancy. These technologies enable the continuous monitoring and real-time data collection, making it easier for healthcare providers to make informed decisions and adjust treatment plans as needed without the necessity of frequent face-to-face visits. This is particularly advantageous for pregnant women, who may find frequent trips to healthcare facilities challenging.

Digital tools, such as mobile apps for tracking symptoms and medication use, as well as wearable devices that monitor respiratory function, can improve patient engagement and self-management. These technologies allow patients to record and report their symptoms in real-time, facilitating timely interventions by healthcare providers. Furthermore, telemedicine provides a platform for virtual consultations, which are crucial during times when access to direct medical care is limited (39,40).

Updates on medication safety and management strategies. Recent advances in research regarding the safety and efficacy of asthma medications during pregnancy have led to significant updates in standard care protocols. These guidelines are critical for ensuring the health and safety of both the mother

and the unborn child. These updated protocols focus on maintaining optimal asthma control by administering the safest possible medications at the lowest effective doses.

The guidelines advocate for a careful assessment of the risks and benefits of each medication, considering the latest evidence on their safety profiles during pregnancy. This approach not only helps in preventing asthma exacerbations, but also minimizes the potential risks associated with medication exposure during pregnancy. The goal is to strike a balance between effective asthma control and the imperative to protect fetal development, thereby reducing the likelihood of complications, such as pre-term birth and a low birth weight associated with poorly controlled asthma. These updated protocols serve as a crucial resource for healthcare providers, ensuring that pregnant women with asthma receive the most effective and safest possible care (41).

Personalized medicine. Personalized medicine represents a transformative approach to healthcare, particularly in the management of asthma during pregnancy, by tailoring treatment to the individual characteristics of each patient. By specifically aligning care with the physiological and genetic profile of pregnant women, this personalized approach enhances the efficacy and safety of asthma management (42).

Pharmacogenomics. The field of pharmacogenomics has emerged as a pivotal component of personalized medicine, providing insight into the genetic factors that influence the onset and progression of asthma, as well as responses to specific therapies. By understanding the genetic makeup of an individual, clinicians can predict how well a patient may respond to certain asthma medications, potentially avoiding ineffective treatments and reducing the likelihood of adverse reactions. For instance, certain genetic markers can indicate a higher likelihood of success with specific bronchodilators or corticosteroids, enabling a more targeted and effective management strategy. This precision in selecting medications is particularly critical during pregnancy, where the safety of drugs becomes even more paramount to avoid any harm to both the mother and the developing fetus (43-45).

Environmental and lifestyle modifications. Environmental and lifestyle factors play a critical role in asthma management. Personalized medicine also includes tailored advice on managing these factors during pregnancy, which can have a profound impact on asthma control (46).

For example, healthcare providers may recommend specific strategies to mitigate exposure to allergens that are known to trigger the asthma symptoms of an individual, such as pet dander, dust mites or pollen. Guidance on avoiding allergens and irritants is essential for managing asthma during pregnancy. This includes practical advice on maintaining a clean, allergen-free home environment, such as strategies to reduce exposure to pet dander, dust mites, and mold. In occupational settings, pregnant women with asthma should receive recommendations on protective measures to minimize exposure to workplace irritants. These proactive measures contribute to controlling symptoms, reducing the risk of exacerbations, and creating a supportive respiratory environment during pregnancy (47,48).

Smoking cessation is critical for pregnant women with asthma as it exacerbates asthma symptoms and poses significant risks to both maternal and fetal health (49). Tailored smoking cessation programs should be readily available, offering support, counseling and resources to help pregnant women quit smoking and adopt a tobacco-free lifestyle. These programs are essential for mitigating the harmful effects of smoking, promoting healthier pregnancies, and lessening the respiratory burden on both the mother and the developing fetus. Healthcare professionals should make it a priority to provide assistance and access to resources for pregnant women to quit smoking. Midwives play a crucial role in this effort by offering guidance, counseling, and resources to support pregnant women in quitting smoking. They can provide personalized care plans, education about the risks of smoking during pregnancy, and ongoing support throughout the quitting process. Additionally, midwives can collaborate with other healthcare providers to ensure that pregnant women have access to comprehensive smoking cessation programs and resources tailored to their specific needs (50-53).

Healthcare professionals play a crucial role in supporting the well-being of pregnant women, particularly those suffering from asthma. Encouraging pregnant women with asthma to receive flu vaccinations is essential for safeguarding their health and the health of their unborn children (54).

Pregnant women, particularly those with asthma, need to be vaccinated against the flu for several reasons. Pregnant women, including those with asthma, are at a higher risk of experiencing severe flu complications due to changes in their immune system and respiratory function during pregnancy. Asthma can further exacerbate these risks, rendering pregnant women more vulnerable to complications, such as pneumonia and respiratory distress. Flu vaccination can help protect pregnant women from contracting the flu, reducing the likelihood of experiencing severe illness and its associated complications. By avoiding the flu, pregnant women can maintain their overall health and well-being during pregnancy. Flu vaccination during pregnancy not only benefits the mother, but also provides protection to the baby. Studies have shown that maternal flu vaccination lowers the risk of flu-related complications in newborns, such as premature birth and low birth weight. Additionally, the response of the mother to the flu vaccine can pass on antibodies to the baby, providing some immunity during the early months of life when the baby is too young for vaccination. Moreover, vaccinating against the flu can help pregnant women with asthma prevent flu-related asthma exacerbations. Respiratory infections, including the flu, can trigger asthma symptoms and lead to the worsening of asthma control. By reducing the risk of flu infection, vaccination can help maintain asthma control and minimize the need for asthma-related medical interventions during pregnancy (55,56).

Healthcare providers can also personalize dietary recommendations to improve respiratory health, including anti-inflammatory foods that aid in managing asthma symptoms. Advice on physical activity, tailored to the condition of the patient and stage of pregnancy, can further support respiratory function and overall well-being (57,58).

Immunological profiling. Immunological profiling is an advanced technique that involves the detailed analysis of

immune markers, such as cytokine levels and other inflammatory indicators, which can vary significantly among individuals. This approach allows clinicians to identify specific inflammatory pathways active in a patient and tailor treatments accordingly. For pregnant women, particularly those with severe or difficult-to-control asthma, this can mean a more precise treatment plan that directly targets the underlying mechanisms of their asthma. By tailoring therapy to the unique immunological profile of each individual, it is possible to achieve better asthma control, reduce the frequency of exacerbations, and minimize the need for systemic medications that may pose risks during pregnancy. This targeted approach ensures that management strategies are both effective and safe, adhering to the principle of 'precision medicine' in a clinical context where both maternal and fetal health are the priority (59).

4. Implications for maternal and fetal health

Maternal outcomes. Effective asthma management during pregnancy is crucial for optimizing maternal health outcomes both during and after pregnancy. Uncontrolled asthma poses significant risks, including increased rates of hypertension and preeclampsia, complications that can lead to further maternal morbidity (60).

Hypertension and preeclampsia. Poorly controlled asthma during pregnancy poses a significant risk for the development of hypertension and preeclampsia in affected women. The inflammatory processes inherent in uncontrolled asthma can potentially lead to vascular dysfunction, thereby exacerbating the risk of hypertensive disorders during pregnancy. Chronic inflammation associated with asthma may disrupt normal vascular homeostasis, leading to endothelial dysfunction and increased vascular resistance, both of which are hallmark features of hypertension and preeclampsia. Furthermore, the systemic inflammatory response characteristic of uncontrolled asthma can promote oxidative stress and endothelial injury, further predisposing pregnant women to developing these complications. In addition, when asthma gets worse, pro-inflammatory cytokines and mediators are released. These can cause endothelial activation and dysfunction, which raises the risk of high blood pressure and preeclampsia (61-63).

A previous meta-analysis revealed that maternal asthma is associated with a 45% higher risk of developing pregnancy-induced hypertension (PIH) [relative risk (RR), 1.45; 95% CI, 1.29-1.63], and the risk of transient hypertension of pregnancy is doubled (RR, 2.00; 95% CI, 1.52-2.63) (58). Additionally, women with asthma have a 28% increased risk of developing preeclampsia or eclampsia (RR, 1.28; 95% CI, 1.25-1.32). Specifically, the risk of developing preeclampsia alone is 43% higher (RR, 1.43; 95% CI, 1.31-1.57) and for eclampsia, it is also 56% higher (RR, 1.56; 95% CI, 1.13-2.15) (62).

Cesarean delivery and complicated labor. Exacerbations of asthma during pregnancy have been associated with increased risks of cesarean delivery and complicated labor. The underlying inflammation and physiological changes caused by asthma can have an impact on labor progression and outcomes (64). A previous study found that 27.1% of pregnant women with asthma who experienced exacerbations underwent cesarean sections, which is significantly higher than the 18.9% rate observed in asthmatic women without exacerbations (65). After excluding cases with direct indications for cesarean sections, such as fetopelvic disproportion or failed induction, the rate still remained higher (7.3 vs. 5.3%) in women with asthma exacerbations (65).

Post-pregnancy recovery. Effective asthma control during pregnancy also affects post-pregnancy recovery, influencing recovery time and the risk of developing postpartum complications. Effective asthma control reduces the risk of developing postpartum hemorrhage and infections, which are more prevalent among women with systemic inflammation due to uncontrolled asthma (66,67). Wang *et al* (62) observed that pregnant women with asthma faced a heightened risk of experiencing deep vein thrombosis (DVT) and pulmonary embolism (PE) compared to those without asthma. More specifically, according to their study, the risk of developing venous thromboembolism was 2.60-fold higher (adjusted OR, 2.60; 95% CI, 2.41-2.80), the risk of developing PE was 3.80-fold higher (adjusted OR, 3.80; 95% CI, 3.41-4.24) and the risk of developing DVT was 2.04-fold higher (adjusted OR, 2.04; 95% CI, 1.84-2.25) in asthmatic women (66). This observation is corroborated by findings of the study by Mendola *et al* (67), which found that women with asthma had a significantly higher risk of developing PE during pregnancy. Specifically, the risk of PE was 1.71-fold higher in women with asthma compared to those without asthma (adjusted OR 1.71, 95% CI, 1.05-2.79) (67).

It is widely recognized that pregnancy inherently entails an increased risk of hypercoagulability and venous stasis, both of which contribute to the development of thromboembolic events (67). Furthermore, asthma itself has been identified as a prothrombotic condition (68).

Impact of pregnancy on asthma. The study conducted by Schatz *et al* (69) involving 330 pregnant women revealed that asthma worsened in 35% of the participants, remained stable in 33% participants and improved in 28% participants (with uncertainty in 4%) during pregnancy.

Stenius-Aarniala *et al* (70), in a prospective study of 504 pregnant women with asthma, noted that 47 women experienced acute attacks, predominantly occurring between the 17th and 24th week of pregnancy. This was attributed to a reduction or cessation of medication early in pregnancy, leading to symptom exacerbation a few weeks later.

In another study, Kim *et al* (65) compared 3,357 pregnant asthmatic patients with 50,355 non-pregnant asthmatic patients, finding a higher rate of asthma-related hospitalizations among pregnant patients, with increasing proportions throughout pregnancy trimesters. They observed a prevalence of 5.3% for asthma exacerbations during pregnancy, with those experiencing acute exacerbations requiring more intensive asthma-related healthcare (65).

Furthermore, another prospective cohort study of 146 asthmatic pregnant women noted severe exacerbations in 36% of cases, with viral respiratory infections and discontinuation of inhaled corticosteroids being major contributing

factors (71). Additionally, psychological changes occurring during pregnancy, such as heightened emotional vulnerability and stress, have been identified as potential triggers for asthma exacerbations (72).

Impact on maternal QoL. The study by Fazel *et al* (73) included 1,603 pregnant women, of whom 34 (2.1%) were diagnosed with asthma. Among these, 38% had well-controlled asthma, while 62% had partly or poorly controlled asthma. Quality of life (QoL) scores varied significantly depending on asthma severity and control. Women with moderate to severe persistent asthma had lower median QoL scores across various domains, including symptoms (39.3 vs. 65.5), activities (58.4 vs. 70.1) and emotional well-being (45.7 vs. 62.9), compared to those with intermittent or mild persistent asthma. The overall QoL was higher in women with well-controlled asthma (median score of 69.6) compared to those with partly or poorly controlled asthma (median score of 55.8) (73). The study by Powell *et al* (74) focused on pregnant women with asthma, examining their QoL and related psychosocial factors. It involved 125 participants with an average age of 28.3 years and a mean gestational age of 16.4 weeks. The Asthma Control Questionnaire (ACQ) revealed that 30.4% of women had controlled asthma, 42.4% had partly controlled asthma and 27.2% had uncontrolled asthma. Their study found that women generally reported a good QoL, with a median Asthma Quality of Life Questionnaire-Marks (AQLQ-M) total score of 0.88 out of 10, indicating relatively low impairment. Anxiety was measured with the Six-Item Short-Form State Trait Anxiety Inventory (STAI-6), where participants had a median score of 26.7, suggesting low anxiety levels. However, a poorer QoL was significantly associated with greater levels of anxiety ($P<0.0001$), more negative illness perceptions, and the need for maintenance with ICS ($P=0.023$) (74).

Fetal outcomes. The impact of asthma on fetal development is profound, with several studies (as presented below) highlighting increased risks of adverse outcomes, such as a low birth weight, preterm birth and perinatal morbidity.

Low birth weight and small for gestational age. Asthma, particularly when poorly controlled, is associated with a higher risk of delivering low birth weight and small for gestational age infants. Active asthma flare-ups during pregnancy raise the risk of these outcomes by affecting fetal growth. This is most likely because of less oxygenation and more stress for the fetus (61,75,76). It has been reported that pregnant women with asthma have a 46% increased risk of delivering a low-birth-weight baby (RR, 1.46; 95% CI, 1.22-1.75) compared to women without asthma. In addition, the risk of having an infant which is small for its gestational age is increased by 22% (RR, 1.22; 95% CI, 1.14-1.31) in women with asthma (75).

Preterm birth. Pregnancies complicated by asthma significantly increase the likelihood of preterm birth, a concerning outcome associated with various maternal and neonatal health risks. It has been reported that the risk of preterm delivery is 41% higher in pregnant women with asthma compared to those without asthma (RR, 1.41; 95% CI, 1.23-1.62) (75). The systemic inflammation characteristic of uncontrolled asthma exacerbations poses a significant threat, as it can trigger a cascade of events leading to the premature onset of labor. Moreover, the hypoxic episodes frequently experienced during asthma exacerbations further compound this risk, potentially disrupting the delicate balance necessary for maintaining the pregnancy to full term. These pathological processes, driven by the inflammatory response and oxygen deprivation inherent in uncontrolled asthma, may ultimately culminate in the untimely initiation of labor, heightening the risk of preterm birth and its associated complications for both mother and baby (77-80).

Perinatal morbidity. Infants born to mothers with asthma face an increased risk of perinatal morbidity, encompassing various health challenges during the immediate newborn period. One significant concern is the heightened incidence of respiratory distress syndrome (RDS), a condition characterized by breathing difficulties shortly after birth due to underdeveloped lungs or inadequate surfactant production. Infants born to mothers with asthma may experience a higher prevalence of RDS due to the potential impact of maternal asthma on fetal lung development and function. Additionally, neonates born to mothers with asthma may require admission to the neonatal intensive care unit (NICU) at a higher rate than infants born to mothers without asthma. Several factors, including the increased likelihood of preterm birth associated with maternal asthma and the potential exacerbation of respiratory symptoms in newborns exposed to maternal asthma triggers or allergens during pregnancy, contribute to this heightened need for NICU admission (81,82).

It has been found that infants born to mothers with asthma have a 49% higher risk of neonatal mortality (RR, 1.49; 95% CI, 1.11-2.00) and a 50% higher risk of requiring NICU admission (RR, 1.50; 95% CI, 1.03-2.20) compared to those born to mothers without asthma. Additionally, the overall risk of perinatal mortality, which includes both stillbirth and neonatal death, is elevated by 25% (RR, 1.25; 95% CI, 1.05-1.50) in this population (82).

Furthermore, maternal asthma exacerbations during pregnancy can lead to fetal hypoxia, which may further compromise the newborn's respiratory function and overall health. The uncontrolled maternal asthma inflammatory milieu may also contribute to systemic inflammation in the neonate, potentially exacerbating respiratory complications and necessitating NICU care (83).

Respiratory conditions in offspring. Children born to mothers with asthma are more likely to develop asthma and other atopic conditions themselves. In the study by Brew *et al* (84), it was reported that children born to mothers with asthma had an increased risk of developing asthma and other atopic conditions. Specifically, maternal asthma was associated with a 1.5- to 2-fold higher likelihood of children developing asthma compared to those whose mothers did not have asthma (84).

The inflammatory processes that connect maternal and childhood asthma are complicated. They involve the immune system of the mother not functioning properly during pregnancy and the development of the immune system of the child after birth. Maternal asthma is associated with increased levels of pro-inflammatory cytokines, such as interleukin (IL)-4, IL-5 and IL-13, which can cross the placenta and influence fetal immune programming. Additionally, maternal asthma

exacerbations during pregnancy may lead to the release of inflammatory mediators and oxidative stress markers, further impacting fetal immune development. These prenatal exposures can prime the fetal immune system towards a Th2-dominant phenotype, characterized by heightened allergic responses and susceptibility to asthma development later in childhood. Moreover, epigenetic modifications, such as DNA methylation and histone acetylation, may occur in response to maternal asthma and contribute to altered gene expression patterns associated with asthma susceptibility in the offspring (84,85).

Neurodevelopmental and behavioral issues. Previous studies have suggested an association between maternal asthma and increased risks of neurodevelopmental disorders in offspring (86,87). It has been found that maternal asthma exacerbations during pregnancy are associated with a 50% increased risk of developing ASD in children (87).

The association between allergy and asthma with neurodevelopmental disorders in offspring implicates intricate mechanisms involving immune dysregulation, inflammatory pathways and potential disruptions in neurodevelopmental processes. Firstly, maternal immune dysregulation, commonly observed in individuals with allergies and asthma, can lead to the release of pro-inflammatory cytokines and chemokines during pregnancy. These inflammatory mediators may traverse the placental barrier and exert direct or indirect effects on fetal neurodevelopment, influencing processes, such as neuronal migration, synaptogenesis and myelination. Additionally, maternal allergic responses may trigger the production of maternal antibodies, including immunoglobulin E (IgE), which could cross the placenta and interact with fetal neural tissues, potentially perturbing normal neurodevelopmental trajectories (88).

Moreover, prenatal exposure to maternal allergic and asthmatic conditions may contribute to oxidative stress and systemic inflammation in the developing fetus, further exacerbating neurodevelopmental vulnerabilities. Oxidative stress markers and inflammatory cytokines released in response to maternal allergic reactions could disrupt delicate neurodevelopmental processes, leading to aberrant synaptic connectivity, altered neurotransmitter signaling, and neuroinflammation in the offspring (86).

Alterations in neural circuitry and immune balance could increase the susceptibility of offspring to neurodevelopmental disorders, including ASD, ADHD and cognitive deficits (89). The intricate association between maternal conditions, such as allergies and asthma and the neurodevelopmental disorders in offspring highlights the necessity of comprehending the fundamental mechanisms. This understanding is crucial for devising specific interventions to reduce these detrimental effects.

Obesity and metabolic syndrome. There is emerging evidence to indicate that children of asthmatic mothers may have a higher risk of developing obesity and metabolic syndrome.

In a previous case-control study involving children aged 6 to 7 years, the researchers aimed to identify factors associated with asthma and obesity in this age group. They collected data on asthma symptoms, maternal and childhood factors and anthropometric measurements. Of the 201 evaluated children, 25.4% displayed asthma symptoms and 37.2% met the classification of being overweight or obese. The group with asthma symptoms and overweight/obesity had higher waist circumference, triceps skinfold, and body mass index compared to those without asthma symptoms. That study found significant associations between asthma and overweight/obesity symptoms and maternal factors. The study specifically identified maternal history of asthma and hypertension during pregnancy as significant risk factors. Children whose mothers had a history of asthma were ~3.73-fold more likely to exhibit asthma and overweight/obesity symptoms, while those whose mothers experienced hypertension during pregnancy had a 3.29-fold higher likelihood of displaying these symptoms (72).

5. Recommendations and future directions

Research gaps. Despite considerable advancements being made in the understanding and management of asthma during pregnancy, significant gaps remain, particularly concerning long-term health impacts and treatment safety. Addressing these gaps is crucial for enhancing patient care and improving outcomes.

Long-term effects on health. There is a need for longitudinal studies that follow children born to mothers with asthma into adulthood to comprehensively assess the long-term health impacts. Such studies are required to focus on the development of chronic diseases, mental health outcomes and the overall QoL. The complex interplay between maternal asthma, environmental factors and genetic predispositions remains poorly understood and warrants further investigation (90).

Safety and efficacy of newer medications. As newer medications and biological treatments become available for asthma management, their safety and efficacy during pregnancy require rigorous evaluation. Small cohorts or post-marketing surveillance reports often limit current data. Large-scale, randomized controlled trials are necessary to establish clear safety profiles and dosing guidelines for these drugs during pregnancy (72).

Research is necessary to determine the impact of varying degrees of asthma severity on pregnancy outcomes. This includes understanding how different levels of disease control may influence both maternal and fetal health and identifying key interventions that could mitigate the risks associated with severe asthma (91).

Emerging technologies. The integration of emerging technologies into asthma management during pregnancy could transform current approaches and enable more personalized and effective care.

Digital health tools. Digital health tools, including mobile health apps and wearable devices, provide promising avenues for real-time monitoring and management of asthma in pregnancy. These tools can facilitate symptom tracking, medication adherence, and the early detection of exacerbations. The potential for these technologies to improve outcomes by

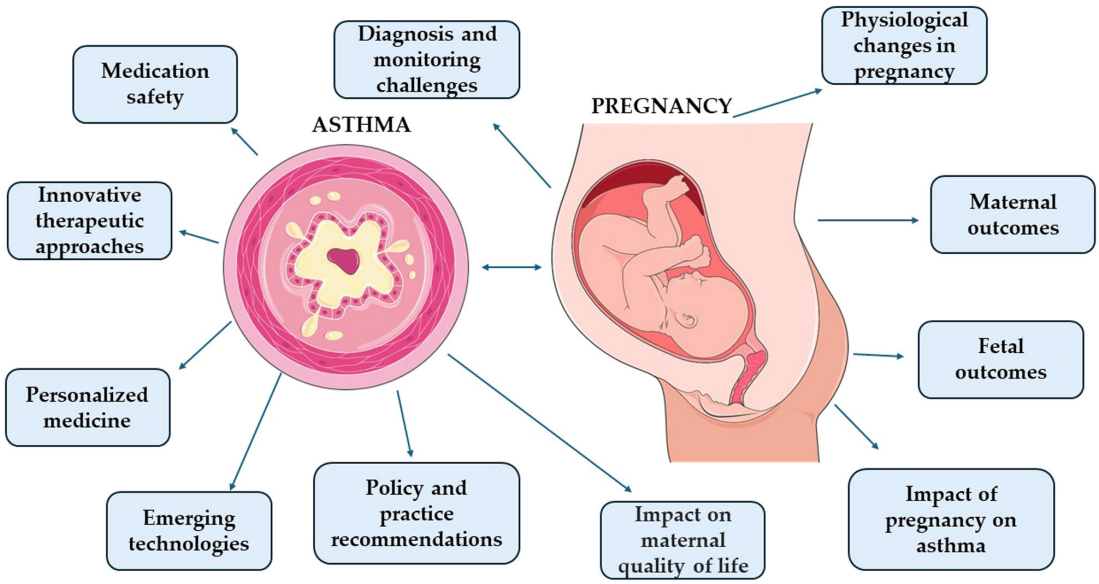

Figure 1. Summary of the complex interplays between asthma and pregnancy. Portions of the figure utilized images from Servier Medical Art, licensed under Creative Commons Attribution 4.0 Unported License.

enhancing patient engagement and enabling more dynamic treatment adjustments has been already highlighted (92).

Telehealth. The expansion of telehealth services can provide pregnant women with better access to specialized care. In rural or underserved areas with limited healthcare resources, this is especially crucial. Telehealth platforms can support regular consultations with healthcare providers, educational initiatives and pulmonary function testing at home, thereby improving asthma management and reducing hospital visits (93,94).

Predictive analytics. Leveraging big data and predictive analytics could lead to more precise predictions of asthma exacerbations and treatment responses in pregnant women. These technologies can analyze vast amounts of data from electronic health records, environmental sensors, and personal devices to identify patterns and predict risks, potentially guiding preventative measures and personalized treatment plans (95,96).

Policy and practice recommendations. To improve asthma management during pregnancy, specific policy adjustments and changes in clinical practice are necessary.

Updated clinical guidelines. There is a need for regularly updated clinical guidelines that incorporate the latest research findings and emerging therapies. These guidelines should provide clear recommendations for managing asthma in different stages of pregnancy and address the use of new medications and technologies (97).

Training and education programs. Enhancing training and education programs for healthcare providers is essential for ensuring they are equipped with the latest knowledge and skills to manage asthma in pregnancy effectively. This includes understanding the pharmacokinetics of asthma medications during pregnancy, applying new technologies, and interpreting data from digital health tools (98).

Policy initiatives. Governments and health organizations need to prioritize funding for asthma research and technology development, focusing on pregnancy-related issues. Additionally, policies that improve air quality and reduce environmental triggers can benefit pregnant women with asthma and contribute to better overall public health outcomes (99,100). The complex interplays between asthma and pregnancy are summarized in Fig. 1.

6. Conclusions

The management of asthma during pregnancy presents unique challenges that significantly impact both maternal and fetal health outcomes. Improved pregnancy outcomes are closely associated with effective asthma control, underscoring the significance of continuous management and monitoring. Recent advancements in medication safety have yielded reassuring data on commonly used asthma treatments during pregnancy, safeguarding both mothers and fetuses from potential adverse effects. Additionally, innovative therapeutic approaches, such as digital health tools and personalized medicine, have shown promising results in improving asthma management in pregnant patients.

However, despite these advancements, substantial research gaps remain, particularly concerning the long-term health implications for children born to mothers with asthma and the safety and efficacy of newer medications. Addressing these gaps through rigorous research and integrating findings into clinical practice is critical for advancing treatment strategies.

Emerging technologies, such as telehealth and predictive analytics offer exciting opportunities to improve asthma care during pregnancy, but their integration into routine clinical practice requires careful consideration and adaptation. Furthermore, policy adjustments and enhanced training programs for healthcare professionals are crucial to ensuring the effective implementation of these new tools and approaches.

In conclusion, ongoing research and adaptation of clinical practices are vital for meeting the evolving challenges of

managing asthma in pregnant patients effectively. Persistence is required in efforts to guarantee optimal care for every pregnant woman with asthma, protecting both the health of the mother and child.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AD and VEG conceptualized the present review. AD, CT, VEG and DAS made substantial contributions to the interpretation and analysis of data from the literature for inclusion in the review, and wrote and prepared the draft of the manuscript. AD and VEG analyzed the data and provided critical revisions. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tool Chat GPT was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention. GINA, Fontana, WI, 2020. https://ginasthma.org/2023-gina-main-report/.
2. Centers for Disease Control and Prevention (CDC): Asthma data, statistics, and surveillance. CDC, Atlanta, GA, 2021. https://www.cdc.gov/asthma/asthmadata.htm#:~:text=The%20current%20asthma%20prevalence%20among,2001%20to%208.0%25%20in%202021. Accessed May 5, 2024.
3. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA and Boulet LP: Global asthma prevalence in adults: Findings from the cross-sectional world health survey. BMC Public Health 12: 204, 2012.
4. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J and Gibson PG: A meta-analysis of adverse perinatal outcomes in women with asthma. BJOG 118: 1314-1323, 2011.
5. Popa M, Peltecu G, Gica N, Ciobanu AM, Botezatu R, Gica C, Steriade A and Panaitescu AM: Asthma in pregnancy. Review of current literature and recommendations. Mædica (Bucur) 16: 80-87, 2021.
6. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C and Schatz M: Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. Eur Respir J 41: 1082-1090, 2013.
7. Schatz M, Dombrowski MP, Wise R, Thom EA, Landon M, Mabie W, Newman RB, Hauth JC, Lindheimer M, Caritis SN, *et al*: Asthma morbidity during pregnancy can be predicted by severity classification. J Allergy Clin Immunol 112: 283-288, 2003.
8. Tam A, Morrish D, Wadsworth S, Dorscheid D, Man SP and Sin DD: The role of female hormones on lung function in chronic lung diseases. BMC Womens Health 11: 24, 2011.
9. To T, Feldman LY, Zhu J and Gershon AS: Asthma health services utilisation before, during and after pregnancy: A population-based cohort study. Eur Respir J 51: 1800209, 2018.
10. Vyawahare AP, Gaidhane A and Wandile B: Asthma in pregnancy: A critical review of impact, management, and outcomes. Cureus 15: e50094, 2023.
11. Costantine MM: Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol 5: 65, 2014.
12. Magon N and Kumar P: Hormones in pregnancy. Niger Med J 53: 179-183, 2012.
13. LoMauro A and Aliverti A: Respiratory physiology of pregnancy: Physiology masterclass. Breathe (Sheff) 11: 297-301, 2015.
14. Palmsten K, Bandoli G, Vazquez-Benitez G, Xi M, Johnson DL, Xu R and Chambers CD: Oral corticosteroid use during pregnancy and risk of preterm birth. Rheumatology (Oxford) 59: 1262-1271, 2020.
15. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L and Petitti D: The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 100: 301-306, 1997.
16. Martel MJ, Rey E, Beauchesne MF, Perreault S, Lefebvre G, Forget A and Blais L: Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. BMJ 330: 230, 2005.
17. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS and Leaderer BP: Asthma symptoms, severity, and drug therapy: A prospective study of effects on 2205 pregnancies. Obstet Gynecol 102: 739-752, 2003.
18. Blais L, Beauchesne MF, Rey E, Malo JL and Forget A: Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. Thorax 62: 320-328, 2007.
19. Bakhireva LN, Jones KL, Schatz M, Johnson D and Chambers CD; Organization Of Teratology Information Services Research Group: Asthma medication use in pregnancy and fetal growth. J Allergy Clin Immunol 116: 503-509, 2005.
20. Otsuka H, Narushima M and Suzuki H: Assessment of inhaled corticosteroid therapy for asthma treatment during pregnancy. Allergol Int 54: 381-386, 2005.
21. Rahimi R, Nikfar S and Abdollahi M: Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: A systematic meta-analysis review. Hum Exp Toxicol 25: 447-452, 2006.
22. Cossette B, Forget A, Beauchesne MF, Rey É, Lemière C, Larivée P, Battista MC and Blais L: Impact of maternal use of asthma-controller therapy on perinatal outcomes. Thorax 68: 724-730, 2013.
23. Eltonsy S, Forget A and Blais L: Beta2-agonists use during pregnancy and the risk of congenital malformations. Birth Defects Res A Clin Mol Teratol 91: 937-947, 2011.
24. Lao TT and Huengsburg M: Labour and delivery in mothers with asthma. Eur J Obstet Gynecol Reprod Biol 35: 183-190, 1990.
25. Lin S, Munsie JP, Herdt-Losavio ML, Bell E, Druschel C, Romitti PA and Olney R; National Birth Defects Prevention Study: Maternal asthma medication use and the risk of gastroschisis. Am J Epidemiol 168: 73-79, 2008.

26. Clifton VL, Rennie N and Murphy VE: Effect of inhaled glucocorticoid treatment on placental 11beta-hydroxysteroid dehydrogenase type 2 activity and neonatal birthweight in pregnancies complicated by asthma. Aust N Z J Obstet Gynaecol 46: 136-140, 2006.
27. Bakhireva LN, Jones KL, Schatz M, Klonoff-Cohen HS, Johnson D, Slymen DJ and Chambers CD; Organization of Teratology Information Specialists Collaborative Research Group: Safety of leukotriene receptor antagonists in pregnancy. J Allergy Clin Immunol 119: 618-625, 2007.
28. Sarkar M, Koren G, Kalra S, Ying A, Smorlesi C, De Santis M, Diav-Citrin O, Avgil M, Lavigne SV, Berkovich M and Einarson A: Montelukast use during pregnancy: A multicentre, prospective, comparative study of infant outcomes. Eur J Clin Pharmacol 65: 1259-1264, 2009.
29. Koren G, Sarkar M and Einarson A: Safety of using montelukast during pregnancy. Can Fam Physician 56: 881-882, 2010.
30. Cavero-Carbonell C, Vinkel-Hansen A, Rabanque-Hernández MJ, Martos C and Garne E: Fetal exposure to montelukast and congenital anomalies: A population-based study in Denmark. Birth Defects Res 109: 452-459, 2017.
31. Hatakeyama S, Goto M, Yamamoto A, Ogura J, Watanabe N, Tsutsumi S, Yakuwa N, Yamane R, Nagase S, Takahashi K, *et al*: The safety of pranlukast and montelukast during the first trimester of pregnancy: A prospective, two-centered cohort study in Japan. Congenit Anom (Kyoto) 62: 161-168, 2022.
32. Tsai HJ, Wu CH, Chang YH and Yao TC: Use of leukotriene-receptor antagonists during pregnancy and risk of neuropsychiatric events in offspring. JAMA Netw Open 6: e231934, 2023.
33. Namazy JA, Cabana MD, Scheuerle AE, Thorp JM Jr, Chen H, Carrigan G, Wang Y, Veith J and Andrews EB: The Xolair pregnancy registry (EXPECT): The safety of omalizumab use during pregnancy. J Allergy Clin Immunol 135: 407-412, 2015.
34. Namazy JA, Blais L, Andrews EB, Scheuerle AE, Cabana MD, Thorp JM, Umetsu DT, Veith JH, Sun D, Kaufman DG, *et al*: Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort. J Allergy Clin Immunol 145: 528-536. e1, 2020.
35. Gemicioğlu B, Yalçin AD, Havlucu Y, Karakaya G, Özdemir L, Keren M, Bavbek S, Ediger D, Oğuzülgen İK, Özşeker ZF and Yorgancıoğlu AA: Country-based report: The safety of omalizumab treatment in pregnant patients with asthma. Turk J Med Sci 51: 2516-2523, 2021.
36. Shakuntulla F and Chiarella SE: Safety of biologics for atopic diseases during pregnancy. J Allergy Clin Immunol Pract 10: 3149-3155, 2022.
37. Murphy VE: Managing asthma in pregnancy. Breathe (Sheff) 11: 258-267, 2015.
38. Lim AS, Stewart K, Abramson MJ, Walker SP, Smith CL and George J: Multidisciplinary approach to management of maternal asthma (MAMMA): A randomized controlled trial. Chest 145: 1046-1054, 2014.
39. Zairina E, Abramson MJ, McDonald CF, Li J, Dharmasiri T, Stewart K, Walker SP, Paul E and George J: Study protocol for a randomised controlled trial evaluating the efficacy of a telehealth program-management of asthma with supportive telehealth of respiratory function in pregnancy (MASTERY©). BMC Pulm Med 15: 84, 2015.
40. Almasi S, Shahbodaghi A and Asadi F: Efficacy of telemedicine for the management of asthma: A systematic review. Tanaffos 21: 132-145, 2022.
41. Labor S, Dalbello Tir AM, Plavec D, Juric I, Roglic M, Pavkov Vukelic J and Labor M: What is safe enough-asthma in pregnancy-a review of current literature and recommendations. Asthma Res Pract 4: 11, 2018.
42. Maier M: Personalized medicine-a tradition in general practice! Eur J Gen Pract 25: 63-64, 2019.
43. Lim C and Priefer R: Pharmacogenomics and pediatric asthmatic medications. J Respir 2: 25-43, 2022.
44. Ferrante G, Fasola S, Malizia V, Licari A, Cilluffo G, Piacentini G and La Grutta S: Pharmacogenomics: A step forward precision medicine in childhood asthma. Genes (Basel) 13: 599, 2022.
45. García-Menaya JM, Cordobés-Durán C, García-Martín E and Agúndez JAG: Pharmacogenetic factors affecting asthma treatment response. Potential implications for drug therapy. Front Pharmacol 10: 520, 2019.
46. Stoodley I, Williams L, Thompson C, Scott H and Wood L: Evidence for lifestyle interventions in asthma. Breathe (Sheff) 15: e50-e61, 2019.
47. Gautier C and Charpin D: Environmental triggers and avoidance in the management of asthma. J Asthma Allergy 10: 47-56, 2017.
48. Nelson HS: Allergen and irritant control: Importance and implementation. Clin Cornerstone 1: 57-68, 1998.
49. Zacharasiewicz A: Maternal smoking in pregnancy and its influence on childhood asthma. ERJ Open Res 2: 00042-2016, 2016.
50. Diamanti A, Papadakis S, Schoretsaniti S, Rovina N, Vivilaki V, Gratziou C and Katsaounou PA: Smoking cessation in pregnancy: An update for maternity care practitioners. Tob Induc Dis 17: 57, 2019.
51. Delakovia T, Sarantaki A, Lykeridou K, Katsaounou P and Diamanti A: Attitudes and knowledge of midwives about smoking cessation perinatally. Eur J Midwifery 7 (Suppl 1): A130, 2023.
52. Georgakopoulou VE and Diamanti A: Artificial intelligence for smoking cessation in pregnancy. Cureus 16: e63732, 2024.
53. Vlachou M, Kirkou G, Vivilaki V, Katsaounou P, Georgakopoulou VE and Diamanti A: Smoking cessation intervention in puerperium: A systematic review and meta-analysis. Pneumon 37: 33, 2024.
54. Taskou C, Sarantaki A, Beloukas A, Georgakopoulou VE, Daskalakis G, Papalexis P and Lykeridou A: Knowledge and attitudes of healthcare professionals regarding perinatal influenza vaccination during the COVID-19 pandemic. Vaccines (Basel) 11: 168, 2023.
55. Marshall H, McMillan M, Andrews RM, Macartney K and Edwards K: Vaccines in pregnancy: The dual benefit for pregnant women and infants. Hum Vaccin Immunother 12: 848-856, 2016.
56. Murphy VE, Powell H, Wark PAB and Gibson PG: A prospective study of respiratory viral infection in pregnant women with and without asthma. Chest 144: 420-427, 2013.
57. Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, Sandel M, Iverson RE Jr, Lee-Paritz A, Strunk RC, *et al*: Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: The VDAART randomized clinical trial. JAMA 315: 362-370, 2016.
58. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R and Wood LG: Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: A randomized trial. Clin Exp Allergy 43: 36-49, 2013.
59. Rupani H, Fong WCG, Kyyaly A and Kurukulaaratchy RJ: Recent insights into the management of inflammation in asthma. J Inflamm Res 14: 4371-4397, 2021.
60. Bonham CA, Patterson KC and Strek ME: Asthma outcomes and management during pregnancy. Chest 153: 515-527, 2018.
61. Abdullah K, Zhu J, Gershon A, Dell S and To T: Effect of asthma exacerbation during pregnancy in women with asthma: A population-based cohort study. Eur Respir J 55: 1901335, 2020.
62. Wang M, He W, Li M, Li F, Jiang L, Wang J, Wang H, Liu X, Yang K and Qiu J: Maternal asthma and the risk of hypertensive disorders of pregnancy: A systematic review and meta-analysis of cohort studies. Hypertens Pregnancy 39: 12-24, 2020.
63. Mirzakhani H, Carey VJ, McElrath TF, Qiu W, Hollis BW, O'Connor GT, Zeiger RS, Bacharier L, Litonjua AA and Weiss ST: Impact of preeclampsia on the relationship between maternal asthma and offspring asthma: an observation from the VDAART clinical trial. Am J Respir Crit Care Med 199: 32-42, 2019.
64. Rejnö G, Lundholm C, Gong T, Larsson K, Saltvedt S and Almqvist C: Asthma during pregnancy in a population-based study-pregnancy complications and adverse perinatal outcomes. PLoS One 9: e104755, 2014.
65. Kim S, Kim J, Park SY, Um HY, Kim K, Kim Y, Park Y, Baek S, Yoon SY, Kwon HS, *et al*: Effect of pregnancy in asthma on health care use and perinatal outcomes. J Allergy Clin Immunol 136: 1215-1223.e1-e6, 2015.
66. Baghlaf H, Spence AR, Czuzoj-Shulman N and Abenhaim HA: Pregnancy outcomes among women with asthma. J Matern Fetal Neonatal Med 32: 1325-1331, 2019.
67. Mendola P, Laughon SK, Männistö TI, Leishear K, Reddy UM, Chen Z and Zhang J: Obstetric complications among US women with asthma. Am J Obstet Gynecol 208: 127.e1-8, 2013.
68. Majoor CJ, Kamphuisen PW, Zwinderman AH, Ten Brinke A, Amelink M, Rijssenbeek-Nouwens L, Sterk PJ, Büller HR and Bel EH: Risk of deep vein thrombosis and pulmonary embolism in asthma. Eur Respir J 42: 655-661, 2013.
69. Schatz M, Harden K, Forsythe A, Chilingar L, Hoffman C, Sperling W and Zeiger RS: The course of asthma during pregnancy, post partum, and with successive pregnancies: A prospective analysis. J Allergy Clin Immunol 81: 509-517, 1988.

70. Stenius-Aarniala BS, Hedman J and Teramo KA: Acute asthma during pregnancy. Thorax 51: 411-414, 1996.
71. Han VX, Patel S, Jones HF, Nielsen TC, Mohammad SS, Hofer MJ, Gold W, Brilot F, Lain SJ, Nassar N and Dale RC: Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders: A systematic review. Transl Psychiatry 11: 71, 2021.
72. Silva BBD, Silva JD, Traebert JL and Schlindwein AD: Maternal and early childhood factors associated with asthma and obesity in children aged 6 to 7 years: A case control study. Einstein (Sao Paulo) 20: eAO5609, 2022.
73. Fazel N, Kundi M, Jensen-Jarolim E, Pali-Schöll IM, Kazemzadeh A, Esmaily H, Abdizadeh MF, Akbarzadeh R, Ahmadi R and Jabbari H: Quality of life and asthma control in pregnant women with asthma. BMC Pulm Med 21: 415, 2021.
74. Powell H, McCaffery K, Murphy VE, Hensley MJ, Clifton VL, Giles W and Gibson PG: Psychosocial outcomes are related to asthma control and quality of life in pregnant women with asthma. J Asthma 48: 1032-1040, 2011.
75. Giles W and Murphy V: Asthma in pregnancy: A review. Obstet Med 6: 58-63, 2013.
76. Goldie MH and Brightling CE: Asthma in pregnancy. Obstetrician Gynaecologist 15: 241-245, 2013.
77. Blais L, Kettani FZ, Forget A, Beauchesne MF and Lemière C: Asthma exacerbations during the first trimester of pregnancy and congenital malformations: Revisiting the association in a large representative cohort. Thorax 70: 647-652, 2015.
78. Vieira AC, Pité H, Morais-Almeida M: Asthma and pregnancy in the 2020 decade: Still a matter of concern. J Matern Fetal Neonatal Med 35: 6498-6504, 2022.
79. Hanania NA and Belfort MA: Acute asthma in pregnancy. Crit Care Med 33 (10 Suppl): S319-S324, 2005.
80. Lao TT and Annie Hui SY: The obstetric aspects of maternal asthma. Best Pract Res Clin Obstet Gynaecol 85 (Pt A): 57-69, 2022.
81. Mendola P, Männistö TI, Leishear K, Reddy UM, Chen Z and Laughon SK: Neonatal health of infants born to mothers with asthma. J Allergy Clin Immunol 133: 85-90.e1, 2014.
82. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C and Schatz M: The risk of congenital malformations, perinatal mortality, and neonatal hospitalisation among pregnant women with asthma: A systematic review and meta-analysis. BJOG 120: 812-822, 2013.
83. Källén B, Rydhstroem H and Aberg A: Asthma during pregnancy-a population based study. Eur J Epidemiol 16: 167-171, 2000.
84. Brew BK, Allen CW, Toelle BG and Marks GB: Systematic review and meta-analysis investigating breast feeding and childhood wheezing illness. Paediatr Perinat Epidemiol 25: 507-518, 2011.
85. Lebold KM, Jacoby DB and Drake MG: Inflammatory mechanisms linking maternal and childhood asthma. J Leukoc Biol 108: 113-121, 2020.
86. Tamayo JM, Rose D, Church JS, Schwartzer JJ and Ashwood P: Maternal allergic asthma induces prenatal neuroinflammation. Brain Sci 12: 1041, 2022.
87. Murphy VE, Gibson P, Talbot PI and Clifton VL: Severe asthma exacerbations during pregnancy. Obstet Gynecol 106 (5 Pt 1): 1046-1054, 2005.
88. Burgess L, McCaffery K, Powell H, Murphy VE, Gibson PG and Turner RM: The influence of asthma control on psychosocial outcomes for pregnant women with asthma. J Asthma 10: 1013-1019, 2015.
89. Cookson H, Granell R, Joinson C, Ben-Shlomo Y and Henderson AJ: Mothers' anxiety during pregnancy is associated with asthma in their children. J Allergy Clin Immunol 123: 847-853.e11, 2009.
90. Fletcher JM, Green JC and Neidell MJ: Long term effects of childhood asthma on adult health. J Health Econ 29: 377-387, 2010.
91. Wang H, Li N and Huang H: Asthma in pregnancy: Pathophysiology, diagnosis, whole-course management, and medication safety. Can Respir J 2020: 9046842, 2020.
92. Tinschert P, Jakob R, Barata F, Kramer JN and Kowatsch T: The potential of mobile apps for improving asthma self-management: A review of publicly available and well-adopted asthma apps. JMIR Mhealth Uhealth 5: e113, 2017.
93. Hawkins SS: Telehealth in the prenatal and postpartum periods. J Obstet Gynecol Neonatal Nurs 52: 264-275, 2023.
94. Morrison D, Wyke S, Agur K, Cameron EJ, Docking RI, Mackenzie AM, McConnachie A, Raghuvir V, Thomson NC and Mair FS: Digital asthma self-management interventions: A systematic review. J Med Internet Res 16: e51, 2014.
95. Molfino NA, Turcatel G and Riskin D: Machine learning approaches to predict asthma exacerbations: A narrative review. Adv Ther 41: 534-552, 2024.
96. Xiong S, Chen W, Jia X, Jia Y and Liu C: Machine learning for prediction of asthma exacerbations among asthmatic patients: A systematic review and meta-analysis. BMC Pulm Med 23: 278, 2023.
97. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, DiMango E, Dixon AE, Elward KS, Hartert T, *et al*: 2020 focused updates to the asthma management guidelines: A report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol 146: 1217-1270, 2020.
98. Yadav P, Jaiswal A, Patel A, Reddy LS and Sindhu AA: A comprehensive review on asthma challenges in pregnancy: Exploring first trimester exacerbations and the spectrum of congenital anomalies. Cureus 15: e49849, 2023.
99. Tiotiu AI, Novakova P, Nedeva D, Chong-Neto HJ, Novakova S, Steiropoulos P and Kowal K: Impact of air pollution on asthma outcomes. Int J Environ Res Public Health 17: 6212, 2020.
100. Kelly FJ, Mudway IS and Fussell JC: Air pollution and asthma: Critical targets for effective action. Pulm Ther 7: 9-24, 2021.