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Oral corticosteroids (OCS), inhaled corticosteroids (ICS), short acting β-2 agonists (SABA), ICS/long acting β-2 agonists (LABA) treatment in pregnancy with asthma: a review

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ABSTRACT

Asthma is one of the common pulmonary disorders that can complicate pregnancy. Therefore, managing asthma is crucial for pregnant women's health and the well-being of the embryo. As consequence, it is important to evaluate the effectiveness and integrity of treatment for this usual therapy in expectant mothers with asthma. This review aimed to analyze the efficacy and safety of OCS, ICS, SABA, and ICS/LABA treatment in pregnancy with asthma. The articles were researched from PubMed, Scopus, and Science Direct as literature resources and selection of process based on inclusion criteria. The use of OCS, ICS, SABA, ICS/LABA were safe for pregnancy with asthma, although there are some side effects. In conclusion, the regiment therapy of asthma in asmathic pregnant women is similar to general treatment for asthmatic.

ABSTRAK

Asma merupakan salah satu gangguan paru yang sering terjadi yang dapat mempersulit kehamilan. Oleh karena itu, manajemen asma perlu diperhatikan karena dapat memperngaruhi kesehatan ibu hamil dan janin. Hal tersebut menjadi hal penting untuk menganalisis efektivitas dan keamanan pengobatan untuk terapi asma pada ibu hamil dengan asma. Tinjauan pustaka ini bertujuan untuk menganalisis efektivitas dan keamanan kortikosteroid oral (OCS), kortikosteroid inhalasi (ICS), β-2 agonis kerja pendek (SABA), dan ICS/pengobatan β-2 agonis kerja panjang (LABA) pada pada pengobatan ibu hamil dengan asma. Artikel dicari dari PubMed, Scopus, dan Science Direct sebagai sumber literatur dan pemilihan proses berdasarkan kriteria inklusi. Penggunaan OCS, ICS, SABA, ICS/LABA pada masa kehamilan relatif aman, meskipun ada kemungkinan efek samping yang timbul. Simpulan, regimen terapi asma pada pada masa kehamilan sama dengan pengobatan asma secara umum.

INTRODUCTION

Asthma is one of the common pulmonary disorders that can complicate pregnancy. the severity of pregnancy-related asthma can change, for the better, moderate, severe or unchanged. Many people with asthma experience worsening of their symptoms during pregnancy because they stop or reduce their usual medications because of concerns for their health and the fetus. Moreover, Exacerbations and untreated asthma can cause difficulties during pregnancy and can increase morbidity and mortality of the expecting mothers and their infants. Therefore, Managing asthma is crucial for pregnant women's health and well-being of the embryo. The risk of asthma problems can be reduced by managing asthma throughout pregnancy.

The aim of efficient pregnant asthma management is to limit recurrence of asthma and avoid exacerbations. This can be fulfilled by trying to avoid symptoms or exacerbations, maintain lung function and normal activity. However, asthma

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is becoming more common and more prevalent, particularly in women who are childbearing age. Consequently, it is crucial that therapy of asthma in pregnancy be followed carefully, and managed appropriately.[2]

Therapy of asthma in pharmacological medications can be generally categorized as acute agents and maintenance agents, or be grouped based on mechanism of action there are anti-inflammatory agents and bronchodilators.[3] The cornerstone of controller therapy during pregnancy is inhaled corticosteroids (ICS) and also inhaled short acting β-2 agonists (SABA) are the primary rescue treatment for pregnant women with asthma. The combination of ICS and long acting β-2 agonists (LABA) is also used in addition to treat asthma. Moreover, oral corticosteroids (OCS) are administered in some patients with severe asthma to achieve adequate asthma control.[4] In consequence of this, it is crucial to analyze the effectiveness and integrity of intervention for this usual therapy in pregnant asthmatic women to meet the goal of managing asthma during pregnancy.

MATERIAL AND METHODS

A systematic search was carried out in the following 3 electronic databases: PubMed, Science Direct, and Scopus to evaluate "asthma management", particularly the use of "inhaled corticosteroids", "short acting β-2 agonists", "inhaled corticosteroid/short acting β-2 agonists combination", and "oral corticosteroids" in the pregnancy population from 2013 to 2022. The medical subject heading (MeSH) terms are "asthma", "pregnancy", "inhaled corticosteroids", "short acting β-2 agonists", "inhaled corticosteroid/long acting β-2 agonists combination", "oral corticosteroids". A total of 101 potentially relevant articles were identified and filtered into 18 excluding the review article type and the article that was not published between 2013 to 2022.

RESULTS

Oral corticosteroids

Pregnancy-related acute asthma exacerbations may be treated with OCS.[2,5] The oral corticosteroid prednisolone, which is primarily used to treat asthma exacerbations, has been demonstrated to be inadequately given in cases of acute asthma exacerbations during pregnancy.[2] Furthermore, OCS consumption in the first three months of pregnancy was linked to an increased possibility of preterm birth in cases of asthma.[6]

Inhaled corticosteroids

Comparative safety studies showed no difference in risk of major malformations between ICS + LABA or high dose ICS monotherapy when used in the first trimester of pregnancy. From 17 published studies are reported the safety of ICS in terms of congenital malformations, and a meta-analysis reported no increased risk of congenital malformations with the use of ICS. Studies show the use of ICS in pregnancy can reduce acute exacerbations and the risk of hospital admission due to recurrence.[7]

Short acting β-2 agonists

The results of research conducted by Davis *et al.*[8] in a cohort study using SABA alone in pregnancy can increase the risk of premature babies. Moreover, combination of SABA + ICS administration in controlling exacerbations to reduce the incidence of preterm infants. There are a difference safety category for pregnancy, several studies show different results of the safety.

Inhaled corticosteroids + long acting β agonists

According to a prior study, pregnant asthmatic women who received

LABA + ICS did not significantly enhance their risk of having serious abnormalities compared to the first three months administration of high-dose ICS monotherapy.[9] Some studies have shown the adverse effects from using combination therapy of ICS/LABA during pregnancy and some have shown that there is no risk combination therapy of ICS/LABA during pregnancy.

DISCUSSION

Pregnancy-related acute asthma exacerbations may be treated with oral OCS.[2,5] One in ten women who are pregnant mostly around the world has asthma, and 10% of these women will experience a severe exacerbation that necessitates OCSs during pregnancy.[2] The oral corticosteroid prednisolone, which is primarily used to treat asthma exacerbations, has been demonstrated to be inadequately given in cases of acute asthma exacerbations during pregnancy, which results in persistent and repeated asthma symptoms two weeks later.[10]

Oral corticosteroids consumption in the first 3 mo of pregnancy was linked to an increased possibility of preterm birth in cases of asthma.[6] Negative perinatal outcomes were more likely in women who used OCS for an asthma exacerbation.[11] Poor symptom management and asthma exacerbations are linked to worse outcomes for both the mother and the child (pre-eclampsia), (preterm birth, underweight babies, and higher perinatal mortality).[12] Therefore, oral corticosteroids are advised when necessary for crucial treatment of severe asthma during pregnancy because these risks would be smaller than the potential dangers of a severe asthma exacerbation that were stated.[4]

Inhaled corticosteroids are used to cure chronic respiratory conditions including asthma. Various inhaled steroid types utilized, such as budesonide, fluticasone propionate, mometasone furoate, and beclomethasone dipropionate.[7] Asthma during pregnancy should be controlled to prevent complications to mother and fetus. Inhalated corticosteroids can be used as an alternative for treatment and safe during pregnancy. Studies show the use of ICS in pregnancy can reduce acute exacerbations and the risk of hospital admission due to recurrence.[7] Other studies also show the use of ICS during pregnancy does not give a bad outcome in the fetus.[13]

There are changes in asthma characteristics in women who use ICS in early pregnancy, where 88% of asthma is well controlled until near delivery, which is characterized by an increase in FEV1 ($p< 0.05$) and a decrease in FeNO ($p< 0.001$).[13] The results of a study from the Swedish Medical Birth Register found that 2968 mothers who took ICS (budesonide) during pregnancy had normal babies. Therefore, the US FDA has assigned a safe category (B) to inhalation and intranasal budesonide.[14]

Comparative safety studies showed no difference in risk of major malformations between ICS + LABA or high dose ICS monotherapy when used in the first trimester of pregnancy. On the contrary, there are limited data of specific safety data of using combination ICS + LABA in second and third trimester. From 17 published studies are reported the safety of ICS in terms of congenital malformations, and a meta-analysis reported no increased risk of congenital malformations with the use of ICS. In another study with animal models show strong teratogenicity of corticosteroids at doses less than or similar to used in human subjects, with cleft palate being the main malformation induced in most species.[15] Therefore, the alternate to minimize ICS exposure and side effect during pregnancy, with reduced the dose of ICS when inflammation or eosinophilic symptoms are low.[15]

Short-acting β-2 agonist drugs are the first line in acute asthma attacks. Short-acting β-2 agonist drugs work by stimulating β-2 receptors involving heterotrimeric G receptors, Gs, and the

effector adenylyl cyclase. The signal generated from these receptors will produce intracellular cyclic adenosine monophosphate (cAMP) through ATP hydrolysis which will then decrease the activity of effectors such as protein kinase A (PKA) Epac. This activation will reduce intracellular Ca^{2+} levels and activate K^{+} channels which cause hyperpolarization of the airway smooth muscle cell membrane which will then cause muscle relaxation.[16] SABA has a fast onset of action (5-15 min) with $t_{1/2}$ short (3-6 hr) so the use of this drug is more recommended in patients with acute asthma attacks.[16] The use of SABA for mild to moderate exacerbations is 2-4 puffs every 20 min at intervals of up to 2 doses.[17]

Short-acting β-2 agonist drugs are included in category C in pregnancy according to the FDA, but the American Congress of Obstetricians and Gynecologists (ACOG) and the National Heart, Lung and Blood Institute (NHLBI) conclude that the use of SABA as an asthma relief reliever is categorized as safe for pregnancy. Meanwhile, according to Australian category A, the use of SABA in pregnant women has not been proven to cause malformations or harmful effects on the fetus.[10]

The results of research conducted by Davis *et al.*[8] in a cohort study using SABA alone in pregnancy can increase the risk of premature babies. Combine administration of SABA with ICS in controlling exacerbations to reduce the incidence of preterm infants. The results of a systematic review conducted by Eltonsy,[9] of 21 studies that examined the effects of using SABA during pregnancy that can cause congenital malformations, fetal growth, and premature birth, there was no increased risk of side effects to the fetus. So the use of SABA drugs is considered safe for pregnant women if used by the required therapeutic dose.

According to GINA, combination ICS and LABA is the primary management to achieve and maintain asthma control (minimize symptoms, activity limitations, bronchoconstriction) and to lower the chances of long-term morbidity and life-threatening exacerbations in the future.[12] The severity of asthma exacerbations can be lessened with ICS/LABA combination therapy as an anti-inflammatory relief and maintenance medication.[18]

Long acting β-2 agonists (e.g formoterol) may enhance the expression of inflammatory genes, and the glucocorticoid budesonide can reverse many of these changes. The addition of a LABA to an inhaled corticosteroid may improve clinical outcomes in asthma due to formoterol's capacity to boost gene induction and repression by budesonide.[19]

Administration of budesonide/formoterol (symbicort) to chicken embryos exhibits teratogenic or lethal effects and develops a malformation. 71% of the living deformed embryos had the gastroschisis effect, and 29% of them had a unilateral or bilateral cleft of the beak. This study was carried out because of a case that occurred in three children with orofacial cleft disorders who were born to a mother who suffered from bronchial asthma and received symbicort in one inhaled dose, 200 μg 2 times a day for all three pregnancies.[19] In a case-control study, using LABA revealed the existence of gastroschisis and cleft palate, while the combined ICS/LABA therapy provided new signs for renal dysplasia.[20] The mechanism of renal dysplasia in combined ICS/LABA still uncertain, but several hypotheses exist. A proportion of the ICS that enters the systemic circulation might cross the placenta and affect the fetus even more rapid than that of other corticosteroids. Moreover, monotherapy of LABA also increase the risk of congenital anomalies which is linked to effects of pregnancy in asthma.[15]

According to a prior study, pregnant asthmatic women who received LABA + ICS did not significantly enhance their risk of having serious abnormalities compared to the first three months

administration of high-dose ICS monotherapy.[15] Some studies have shown the adverse effects from using combination therapy of ICS/LABA during pregnancy and some have shown that there is no risk combination therapy of ICS/LABA during pregnancy. Previous study conducted in monotherapy either ICS or LABA alone. Even so, the research related to the combination therapy of ICS/LABA in asmathic pregnant women is still limited.

CONCLUSION

The regiment therapy of asthma in asmathic pregnant women is similar to general treatment for asthmatic. The use of OCS, ICS, SABA, and ICS/LAB are safe for pregnancy with asthma although there are some side effects happened. Moreover, for efficacy, oral corticosteroids especially use in severe asthma with exacerbation. The SBA and ICS are used to treat exacerbation and ICS/LABA combinations for reliever and maintenance. More research should be conducted to evaluate another side effects that might happen in pregnancy women and fetus.

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