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REVIEW

Beta$_2$-agonists use during pregnancy and perinatal outcomes: A systematic review

Sherif Eltonsy [a,b], Fatima-Zohra Kettani [a,b], Lucie Blais [a,b,*]

[a] *Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, Canada*
[b] *Hôpital du Sacré-Cœur de Montréal, Montreal, Quebec, Canada*

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Summary
Background: Short and long-acting beta$_2$-agonists (SABA and LABA) have a crucial role in asthma management during pregnancy, as stated in the current guidelines.
Objective: To systematically review the evidence on beta$_2$-agonists use during pregnancy and adverse perinatal outcomes.
Data sources and study selection: Six databases were searched before January 1, 2013 for beta$_2$-agonists use during pregnancy and congenital malformations, small for gestational age, mean and low birth weight, gestational age and preterm delivery. Original English language articles were included with no cut-off date. Quality assessment and post-hoc power calculations were performed.
Results: Twenty-one original studies were identified. Four studies reported a significant increased risk of congenital malformations with SABA, while one study reported a significant decreased risk with high doses of SABA. One study reported a significant increased risk of congenital malformations with LABA and four studies reported a significant increased risk of congenital malformations with beta$_2$-agonists (SABA and/or LABA). One study reported a decrease in birth weight centiles among LABA users.
Limitations: All studies reporting significant results, except two, used non-asthmatic women as reference group, making it difficult to differentiate between the effect of the disease from the one of the beta$_2$-agonists. Non-significant results should be interpreted with caution due to the low statistical power of several studies.
Conclusion: Methodological limitations and lack of power of several studies prevent us to conclude on the perinatal safety of beta$_2$-agonists. Until further evidence is available, physicians should continue prescribing them as recommended in the guidelines whenever needed to attain asthma control.

* Corresponding author. Université de Montréal, Faculté de pharmacie, C.P. 6128, succursale Centre-ville, Montreal, Quebec H3C 3J7, Canada. Tel.: +1 514 343 6111 extension 3786; fax: +1 514 343 6057.
E-mail address: lucie.blais@umontreal.ca (L. Blais).

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Contents

Introduction

Asthma is considered to be one of the most common chronic diseases among pregnant women, affecting approximately 4–8% of the pregnancies in the United States and even higher among other populations [1–3]. Pregnant women with severe or uncontrolled asthma are at higher risk for pregnancy complications and adverse fetal outcomes than women with well-controlled asthma [2,4–8]. Due to the reported potential risk of uncontrolled asthma during pregnancy on the health of the mother and fetus, the National Asthma Education and Prevention Program (NAEPP) states that "(…) it is safer for pregnant women with asthma to be treated with asthma medications than it is for them to have asthma symptoms and exacerbations." [2]

While inhaled corticosteroids (ICS) are considered the cornerstone therapy in the management of persistent asthma during pregnancy [9,10], beta$_2$-agonists have a crucial role in asthma management [2]. During pregnancy, short-acting beta$_2$-agonists (SABA) are used as reliever medications for all asthma types (mild, moderate, or severe), while long-acting beta$_2$-agonists (LABA) are used in cases of moderate to severe persistent asthma, in combination with low or medium doses ofICS [2,11]. It has been reported that 40–70% of asthmatic women use SABA and 8–13% use LABA during pregnancy [12,13]. Despite being widely used during pregnancy, all of the SABA and LABA are classified as "C" under the US Food and Drug Administration (FDA) categorization [4], which states that risk cannot be ruled out and that there is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk. Moreover, the Teratogen Information System (TERIS) reports that SABA and LABA have an "Undetermined" teratogenic risk due to the limited quality and quantity of data on the safety of these medications [4].

Several studies examined the effect of SABA and LABA use on perinatal outcomes during pregnancy [2,14–24]. Published reviews on this topic did not capture the whole evidence from all published studies on all clinically important perinatal outcomes [4,14–16,25,26]. Given the need to better estimate their fetal risks, we aimed to summarize the existing human data – from experimental trials and observational studies – examining the impact of the use of inhaled SABA and LABA for the treatment of asthma during pregnancy on several perinatal outcomes, which are major and any congenital malformations, small for gestational age (SGA; weight $\leq$10th percentile for the gestational age), birth weight, low birth weight (LBW; weight $<$2500 g), gestational age and preterm delivery. We also assessed the quality of each study using a validated quality assessment scale and performed post-hoc power calculations to evaluate the capacity of the studies to detect clinically relevant effects.

Methods

Data sources and search strategy

A search strategy was formed, registered and published (PROSPERO 2011: CRD42011001554, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?

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