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REVIEW

PNEUMOLAB PROCEEDINGS 9

# Asthma in pregnancy: one more piece of the puzzle

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## ABSTRACT

Asthma is the most commonly occurring respiratory complication during pregnancy, and is associated with a wide range of adverse maternal and perinatal outcomes. However, there is strong evidence that an adequate control of asthma can improve the health of both mothers and their babies. Despite the well-known risks of poorly-controlled asthma during pregnancy, a large proportion of women have sub-optimal asthma control, due to concerns surrounding risks related to pharmacological agents and uncertainties regarding the effectiveness and safety of different management strategies.

A recent retrospective study showed that step-up therapy with low-dose inhaled corticosteroids / long-acting β2-agonist inhalers (ICS/LABA) or high-dose ICS presents the same risk profile in terms of major congenital malformations.

These results are consistent with asthma management guidelines and provide scientific evidence to help physicians and mothers make evidence-based treatment decisions during pregnancy, particularly when stepping up to higher doses of ICS or addition of a LABA are required. These reassuring results should encourage women to continue their asthma medications when required to control their asthma during pregnancy and increase the likelihood of healthy pregnancies and newborns. This commentary focuses on some critical issues of this recent work and to the need of future study to evaluate the safety during pregnancy of novel molecules recently introduced for asthma treatment.

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Asthma is the most commonly occurring respiratory disorder during pregnancy, and is associated with a range of adverse maternal and perinatal outcomes.[1] There is strong evidence however, that an adequate control of asthma can improve the health of both mothers and their babies.[2, 3] Despite the well-known risks of poorly-controlled asthma during pregnancy, a large proportion of women have sub-optimal asthma control, due to concerns surrounding risks of pharmacological agents, and uncertainties regarding the effectiveness and safety of different management strategies.[1]

## Asthma management in pregnancy and congenital malformations

The work of Eltonsy *et al.*[4] tries to help the choice for better treatment of asthma during pregnancy between high dose inhaled corticosteroids (ICS) and long-acting β2-agonist (LABA)/low dose ICS combination by comparing the risk of major congenital malformations in asthmatic women exposed to this two treatment strategies during the first trimester of pregnancy.

International guidelines on asthma under-

line the importance to maintain asthma treatment during pregnancy and affirm the importance of the good control of the disease, suggesting that the benefit from taking the right dosage of drugs overcomes the risk of maternal and fetal complications.[5, 6]

However, so far there is no indication, in terms of safety, about which could be the best step-up strategy from step 2 to step 3 between increasing ICS dose and introducing LABA therapy.

Estimates from published studies suggest that the asthma affects about 3-14% of pregnancies,[7-10] reporting a common use of asthma medications during this period. There are also a number of physiological and mechanical changes during pregnancy that might cause either improvement or worsening (including exacerbations) of asthma symptoms.[11-13]

Recently, the following problems associated with asthma during pregnancy have been reported: 1) an increased risk of low birth weight and small dimensions for gestational age among females with moderate-to-severe asthma and acute exacerbations during pregnancy; 2) an increased risk of preterm birth associated in particular with oral steroid use; 3) a small but statistically significant increased risk of congenital malformations, particularly of cleft lip with or without cleft palate; 4) an increased risk of neonatal hospitalization and death.[14]

Some data suggesting cleft lip and palate risks with oral corticosteroid exposure implied a possible hazard of ICSs.[15]

In only one study a weak association between ICS use and relatively severe cardiac defects, orofacial clefts and anal atresia was noted.[16]

In a recent systematic review were examined 21 studies on the effect of $\beta_2$-agonists use during pregnancy. The authors found evidence of increased risk of congenital malformations after pregnancy exposure to fenoterol, a short-acting $\beta_2$-agonist (SABA) in one study and LABA in another study. No increased risk was found for the other outcomes, except a decrease in birth weight centiles among salmeterol (LABA) users. However, non-significant results should be interpreted with caution, since a large percentage of the negative studies were underpowered to detect clinically significant effects.[17]

The work of Eltonsy *et al.*[4] demonstrates that the risk of major congenital malformations was not higher among asthmatic pregnant women treated with a LABA plus ICS combination therapy than among women treated with an ICS monotherapy at a higher dose during the first trimester. These results are consistent with asthma management guidelines and provide scientific evidence to help physicians and mothers make evidence-based treatment decisions during pregnancy, particularly when a step up to higher doses of ICS or addition of a LABA is required. These reassuring results should encourage women to continue to take their asthma medications when required to control their asthma during pregnancy, and, as suggested by previous research evidence, this will increase the likelihood of healthy pregnancies and newborns. With substantial evidence suggesting poor maternofetal outcomes with uncontrolled asthma and newer data that largely lack any consistent evidence for teratogenicity, or at least for difference in terms of teratogenicity of two different approaches, the asthma community needs to redouble its efforts to promote medication adherence because it is safer for pregnant women with asthma to be treated with asthma medications than to expose themselves to the risks of an uncontrolled asthma.

The study by Eltonsy *et al.*[4] has the strength of being based on established electronic medical records that allowed to access more than 27,000 pregnancies in asthmatic women who delivered between 1990 e 2009 in Québec. From this population, the authors could establish two sub-cohorts of pregnancies in moderate asthma and in severe asthma. The women's exposure to asthma medications during pregnancy was assessed through the prescriptions of medications dispensed in community pharmacies; these data were prospectively collected independently of the outcome, avoiding any recall bias.

Such as other retrospective fetal safety studies, this work lacks of some considerations. The nature of the design does not allow to easily address confounding factors, such as alcohol, antenatal care and environmental teratogens, potentially affecting both exposure and outcome. Moreover, the data do not report the eventual difference between different LABAs, so risks specific to a single drug might be overlooked when a pharmaceutical class as a whole is studied.

These large and long-duration studies risk to remain underpowered because they could even miss some events, such as occult and delayed diagnosis of malformation and non-viable malformations resulting in miscarriages.

The study seems to suffer from non-trivial limitations in the scientific interpretation of the findings and the speculation over them. One interesting issue that comes out from the current investigation is that the receipt of social assistance during pregnancy was associated with an increased risk of major malformations. What does it mean? The authors seem not to have lingered very long on this aspect. Is it all related to non-pharmacological factors? And if so, what is the rationale of having increased risk of malformations when social assistance is in place? This is an intriguing topic that deserves more attention. Moreover, it looks like the risk of premature delivery is not addressed. The occurrence of malformations may obviously be not different between the two regimens, but premature delivery is another piece of the puzzle that need to be put in place, and properly evaluated. Finally, the study reassures on the safety (and lack of difference) between the two regimens and now calls for head-to head clinical trials to assess for efficacy as well.

## Conclusions

Some issues should be addressed. There is the need of data on the new antiasthmatic drugs, such as vilanterol ad fluticasone furoate, a new ICS/LABA fix dose combination, because their safety has not been established yet. Although no teratogenicity interactions between fluticasone and vilanterol were seen in animals at the maximum human daily inhalation dose alone or in combination, their use in pregnancy is currently not recommended.

Future studies should be large enough to be able to compare equivalent treatment regimens, or to compare different molecules of a class in order to minimize confounding by asthma severity and to identify the safest treatment options. Future studies might also consider meta-analysis of drug-specific effects from several well conducted large studies.

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