

Treatment of asthma during pregnancy: more solid evidence needed

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In this issue of *Thorax*, a paper by Tata and colleagues¹ assesses the association between maternal asthma and gestational exposure and asthma medications with the risk of congenital malformation in offspring using The Health Improvement Network primary care database (see page 981). Their findings showed that gestational exposure to commonly used asthma medications seems to be safe, although a moderate teratogenic risk of cromones cannot be excluded. This is important information for many doctors, mainly pulmonologists and allergologists involved in the treatment of asthma in pregnant women. It indicates that we can approach the pregnant patient with asthma in the traditional manner, without major concerns and using all the available treatment options with the exclusion of cromones which, in any case, currently represent an unusual therapeutic choice.

The results of this study enable us to reassure our pregnant patients. We have all found that one of the most complicated aspects of the work of a chest physician is to convince a pregnant patient with asthma to adhere to prescribed therapy. Several surveys have shown that women decrease and/or stop asthma medications during early pregnancy, probably because they are concerned about the safety of asthma medications during pregnancy.²⁻⁴ Conversely, physicians appear to be reluctant to prescribe asthma medications for pregnant women. A multicentre study found that pregnant women with asthma were significantly less likely to be prescribed corticosteroids in the emergency department: only 44% of pregnant women were treated with corticosteroids

compared with 66% of non-pregnant women.⁵ Those who were admitted to hospital were less likely to be treated with corticosteroids at discharge and were almost three times more likely to experience a subsequent exacerbation than non-pregnant women.⁵ This is undoubtedly an important issue given that it is estimated that about 18% of all pregnant women with asthma have at least one visit to the emergency department and as many as 62% of pregnant subjects with acute severe asthma require hospitalisation.⁶

In theory, pregnant women should not receive drugs, especially during the first 3 months of gestation. In reality, however, asthma in pregnancy needs to be treated and drugs are necessary, since uncontrolled asthma represents a risk factor to both the mother and the fetus.⁷ Murphy *et al*⁸ recently conducted a systematic review of the literature for publications related to exacerbations during pregnancy. During pregnancy, exacerbations of asthma which require medical intervention occur in about 20% of women, with approximately 6% of women being admitted to hospital. Women who have a severe exacerbation during pregnancy are at a significantly increased risk of having a low birthweight baby compared with women without asthma, which may predispose to diseases in later life. On the other hand, adequately controlled asthma does not seem to be associated with adverse maternal and fetal outcomes. Consequently, US guidelines for the management of asthma during pregnancy⁹ recommend a stepwise approach to treatment with the goal of maintaining control of maternal asthma, as the risks of asthma exacerbations are greater than the risks associated with the use of asthma medications during pregnancy. In effect, increasing evidence supports the perception of the safety of inhaled corticosteroids for the treatment of asthma during pregnancy with regard to the likelihood of congenital malformation.¹⁰ Moreover, use of inhaled β agonists, inhaled corticosteroids and

theophylline do not appear to increase perinatal risks in pregnant women with asthma, whereas oral corticosteroid use seems to be significantly associated with preterm birth at less than 37 weeks' gestation.¹¹

It is not clear whether oral corticosteroids directly cause premature birth or whether they serve as a marker for asthma sufficiently severe or uncontrolled to cause prematurity.¹¹ However, this is unimportant because systemic corticosteroids, intravenous or oral, should be administered to patients suffering from an acute asthma exacerbation who show no improvement with the initial bronchodilator therapy and almost always to those with moderate to severe exacerbations.¹² In any case, the British Thoracic Society guidelines¹³ clearly state that medical management is identical for pregnant and non-pregnant women and oral steroids should be given in appropriate doses if clinically indicated. This need for systemic corticosteroids strengthens our opinion that complete control of symptoms and prevention of exacerbations must be the primary objectives when managing a pregnant patient with asthma.¹⁴

However, many reports have documented the risks associated with the use of asthma medications during pregnancy. A population-based case-control study that included cases of orofacial clefts, conotruncal heart defects, neural tube defects and limb reduction defects suggested a possible causal association between cleft lip and palate and maternal corticosteroid use during the periconceptional period (1 month before to 3 months after conception).¹⁵ Moreover, in another controlled study, the risk of gastroschisis in the offspring of women treated with bronchodilators during the periconceptional period was approximately twice that of women not using bronchodilators.¹⁶ This positive association persisted when women taking these medications outside the periconceptional period were added to the reference group.¹⁶ A recent analysis of data extracted from the Swedish Medical Birth Register identified 24 369 women with 24 750 infants who reported the use of anti-asthma drugs at the first maternal healthcare visit (usually weeks 10–12) and 7778 women with 7963 infants who received a prescription for anti-asthma drugs during pregnancy from a maternal healthcare centre. A number of negative effects were reported in the neonate when the mother used anti-asthma drugs during pregnancy, all of which were relatively severe. These

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included preterm birth, low birth weight, small-for-gestational age and neonatal symptoms of icterus, hypoglycaemia and respiratory problems.¹⁷ The same analysis showed an increased risk of congenital malformation among infants born to women who used anti-asthma drugs in early pregnancy. The increase in risk was small and it is unclear if it was due to the asthma itself, to residual confounding, or to the drugs used. It seemed to occur mainly in women who used three or more anti-asthma drugs and therefore probably had relatively severe asthma.¹⁸ The increase in malformation rate appears to be associated with three conditions: relatively severe heart defects, orofacial clefts (notably median cleft palate) and anal atresia.¹⁸ These findings indicate that there is an effect, although small, on the infants of mothers who use anti-asthma drugs during pregnancy.

There is a need for more solid evidence but, unfortunately, there is limited information on the long-term efficacy and safety of currently approved asthma medications in pregnant subjects, largely because traditional double-blind placebo-controlled research is unethical in pregnant women. Given the lack of current and valid data, we believe that no correct implications for practice can be drawn from systematic reviews.

The lack of certainty about how to treat a pregnant patient with asthma leaves us in doubt as to what to do, for the obvious ethical but also legal implications of our choices. Nonetheless, we believe that uncontrolled asthma in pregnant women can result in perinatal complications and exacerbations which can be life-threatening for the mother and fetus. Because these risks are greater than those of the adverse effects caused by

controller medication use, we strongly support the opinion that women with asthma should receive controller therapy during pregnancy. In effect, this is what we do in everyday practice, fortunately without any negative result, at least until today, probably because we only prescribe those asthma controller medications that fall within pregnancy category B and only long-acting β_2 agonists between those that fall within pregnancy category C of the US Food and Drug Administration (FDA) pregnancy category ratings for asthma controller medications.¹⁹ The paper by Tata and colleagues¹ supports our behaviour, with the exception of cromones which have been rated pregnancy category B by the FDA based primarily on safety in animal reproduction studies. However, this is not an important issue because cromones have not been prescribed for a long time.

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