

Asthma drugs in pregnancy and lactation

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SUMMARY

Uncontrolled asthma during pregnancy poses many short and long-term risks to the mother and her baby. Maintaining optimal asthma control is important during pregnancy, but studies of drug safety are limited.

Inhaled short-acting beta agonists are safe to prescribe throughout pregnancy. Long-acting beta agonists need not be stopped in the first trimester and can be used in the second and third trimesters if needed to maintain adequate asthma control.

Inhaled corticosteroids, particularly budesonide, at recommended doses are safe to use during pregnancy and breastfeeding. Oral corticosteroids, at the doses used to treat asthma exacerbations, do not appear to pose a significant risk to the mother or child.

Pregnant women tend to overestimate the risk of using asthma drugs, but they are often unaware of the greater risks of uncontrolled asthma. They put themselves at unnecessary risk of acute exacerbations by discontinuing or reducing therapy.

Women with asthma should be advised to continue to take their treatment while breastfeeding. Spacing the dose and feed time may be necessary when using oral corticosteroids.

Introduction

Approximately 8–13% of pregnant women have asthma.¹ Asthma control varies during pregnancy, but it can deteriorate in over one third of women.² Continuing therapy and monitoring is essential during pregnancy to maintain optimal control and prevent acute exacerbations. Pregnant women often accept frequent symptoms at the expense of less medication, but underestimate the harm an exacerbation may have on the pregnancy.

There are limited well-designed studies about asthma drugs during pregnancy and breastfeeding. The studies that assessed safety did not assess the drugs

individually and rarely controlled for other drugs or medical conditions. Adverse events have also been attributed to worsening asthma, rather than its treatment.

In contrast, there is ample evidence of the risks associated with poorly controlled asthma during pregnancy.³ These include an increased risk of preterm births, low birthweight, pre-eclampsia, malformations and poor fetal brain development.³⁻⁵ Survivors of preterm birth and fetal growth restriction face an increased risk of cardiovascular complications in later life.⁶ Optimal asthma control is therefore vital during pregnancy and a harm-benefit assessment should be done for each patient.

Women with asthma who smoke should be encouraged to quit as smoking can reduce their response to preventive therapy.⁷

Non-adherence to asthma treatment

Almost a third of pregnant women discontinue or reduce their asthma preventing drugs during pregnancy and overcompensate with short-acting relieving drugs.¹ This jeopardises asthma control. The connotations of the word 'steroid' distress many women and they overestimate the harm steroids could have on their unborn child.⁸ In addition, women who are unaware of the risks of poorly controlled asthma and not properly advised turn to unreliable resources, such as the internet, which often exaggerate the risks of treatment without highlighting its benefits.⁸

The uncertainty and anxiety surrounding the treatment of asthma during pregnancy emphasises the important roles of doctors, pharmacists, asthma educators and midwives in encouraging adherence to treatment. The first antenatal visit is an opportunity to discuss the benefits of continuing treatment and to review the patient's asthma management plan.⁹ Any harmful effects from the drugs used to prevent asthma will be outweighed by maintaining good control and avoiding acute exacerbations.

Inhaled beta agonists

Salbutamol and terbutaline are safe to use during pregnancy.¹⁰ In the Australian categorisation of risk they are classified as category A (Table)¹¹

Limited studies are available on long-acting beta agonists such as salmeterol and eformoterol,¹² which are thus categorised as B3 (Table). As the majority of these studies analysed long-acting beta agonists in

combination with other asthma drugs and have not shown any significant increase in harm, they are unlikely to pose a risk.¹² Furthermore, maternal plasma concentrations after inhaled salmeterol or eformoterol are very low or virtually undetectable.¹³ The Asthma Management Handbook discourages starting treatment with long-acting beta agonists in the first trimester, but does not advocate withdrawing them if they are necessary to control the patient's symptoms.¹⁴

Inhaled corticosteroids

Using inhaled corticosteroids during pregnancy has been associated with a decreased risk of low birthweight babies.¹⁵ A study of women with asthma exacerbations found a 55% reduction in subsequent exacerbations and hospital admissions in those who used beclomethasone compared to those who did not.¹⁶ Women should be advised to continue their preventive drugs during pregnancy.

Budesonide is a category A drug. The Asthma Management Handbook recommends switching to budesonide before pregnancy.¹⁴ Ciclesonide, fluticasone and beclomethasone are category B3

(Table) with less evidence for safety during pregnancy.

Comparisons between different inhaled corticosteroids and doses are limited. In one study including beclomethasone, budesonide and fluticasone, women who used more than 1000 microgram daily in the first trimester were more likely to have a baby with congenital malformations (relative risk 1.63; 95% confidence interval 1.02-2.60).¹⁷ However women on high-dose inhaled corticosteroids were likely to have more severe asthma, so adverse outcomes could have been associated with worsening asthma and oral corticosteroid use.¹² The negative outcomes reported should not discourage prescribers from increasing the dose of inhaled corticosteroids when necessary, as the risks of harm may be greater if the patient has uncontrolled asthma. Before increasing the dose it is important to check the patient's adherence and inhaler technique. The relationship between gestation and adverse events has not been explored in depth, but available studies suggest there is no greater risk with using inhaled corticosteroids in any particular trimester.¹²

Table Australian categorisation of risk of asthma drugs in pregnancy ¹¹

Category	Definition	Drugs
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed	budesonide terbutaline salbutamol prednisolone
B1	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.	nedocromil montelukast sodium cromoglycate
B2	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals are inadequate or may be lacking, but available evidence show no evidence of an increased occurrence of fetal damage.	
B3	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.	beclomethasone ciclesonide fluticasone eformoterol salmeterol
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.	
D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.	
X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy	

Oral corticosteroids

Prednisolone, the oral corticosteroid mainly used in the treatment of exacerbations of asthma, has been shown to be under-prescribed in acute asthma exacerbations during pregnancy, leading to persistent and recurrent asthma symptoms two weeks later.¹⁸ The risk of poorly-controlled asthma and the potential for another acute exacerbation during pregnancy is dangerous and acute asthma needs to be treated adequately.

There have been reports of an increased risk of cleft lip with or without cleft palate from first trimester use, however, the data were from studies with a small sample size that included corticosteroid use for other conditions that generally needed higher and more frequent doses.¹⁹ It is also difficult to separate the potential effects of oral corticosteroids from the potential effects of poorly controlled maternal asthma as oral corticosteroids are generally indicated for severe asthma.

It is necessary to monitor blood glucose if oral corticosteroids are used in pregnancy, especially if there is gestational diabetes.

Cromolyns and leukotriene receptor antagonists

Inhaled cromolyns are probably safe to use in pregnancy.¹⁰ No well-designed studies have assessed the sole use of leukotriene receptor antagonists, such as montelukast, during pregnancy. Studies have shown an increase in adverse events with use, but these studies did not exclusively test montelukast during pregnancy.¹² Montelukast should be used in pregnancy only if clearly indicated and only after considering more effective and safer treatment, especially given its prescribing restrictions in the Pharmaceutical Benefits Scheme.¹⁰

Anticholinergics

Currently there are no published controlled data on the use of inhaled anticholinergics during pregnancy and their use should be reserved as a last option. Nebulised ipratropium bromide with inhaled beta agonists and intravenous corticosteroids has been recommended for management of acute asthma during pregnancy.²⁰

Lactation

Asthma control in the postpartum period is important for the same reasons as it is in healthy, non-pregnant women, and the exacerbation risk is similar in the two groups of women. There are limited studies about the safety of asthma drugs during breastfeeding. Published studies in the postpartum period have been small case series with generally short follow-up.

Systemic absorption of inhaled drugs is generally minimal and causes little harm to the infant.¹⁴ The infant's exposure is 10 to 1000 times less than during pregnancy.²¹ The amount ingested through the mother's milk is far below the therapeutic level for an infant – mostly under 3% of a therapeutic dose per kilogram bodyweight.²²

Short-acting beta agonists may be used at the usual doses.¹⁰ Maintenance doses of inhaled budesonide (200 microgram or 400 microgram twice daily) result in negligible systemic exposure for the breastfed infant.²³ Once absorbed, inhaled budesonide is a weak systemic steroid and it is unlikely that clinically relevant concentrations would be transferred to the infant.¹³ Similarly, only 30% of fluticasone is absorbed systemically and the majority is metabolised by first-pass metabolism.²⁴ No studies are available for the safety of ciclesonide and cromolyn (milk:plasma ratios unknown) in breastfeeding mothers, but in vitro studies show that the infant would be exposed to virtually undetectable concentrations so is unlikely to be at risk.¹³

There are no human studies of montelukast in breastfeeding, but animal studies have detected excretion into milk. Alternative treatment with short-acting beta agonists, long-acting beta agonists or inhaled corticosteroids should be considered during breastfeeding, particularly as montelukast is taken orally.¹⁰

Prednisolone at recommended doses is thought to be safe since the amount excreted in human milk is low with daily doses up to 80 mg. It is recommended to withhold feeds for four hours after each dose to reduce infant exposure. Prednisolone is preferred over prednisone, as prednisone is converted to prednisolone in vivo, causing a double peak of parent medicine and metabolite.¹⁰

Conclusion and recommendations

Due to the limited evidence from large, well-designed prospective studies in pregnant and breastfeeding women, there is often a lack of confidence amongst health professionals when deciding the most appropriate asthma therapy. Optimal asthma control should always be the first priority.

Australian and international guidelines recommend that women continue with the same therapy they used before pregnancy, especially if this regimen adequately controlled their asthma, and that they monitor their asthma monthly.^{14,25-27} A switch to budesonide could be considered if the patient is planning a pregnancy and is already taking another inhaled corticosteroid.¹⁴

Most of the asthma drugs are safe to use in breastfeeding. Women should be encouraged to continue their treatment during lactation.

Severe or difficult to treat asthma and asthma in women who continue to smoke may require a multidisciplinary approach with a respiratory specialist and more intensive monitoring.

Researchers are currently looking into markers of asthma control during pregnancy.²⁸ For now, spirometry is recommended for monitoring during pregnancy.²⁹ ◀

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SELF-TEST QUESTIONS

True or false?

- The risk of fetal malformations is increased by treating acute exacerbations of asthma with oral corticosteroids.
- Inhaled budesonide can be used during lactation.

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