PREGNANCY PLUS

Asthma in pregnancy

Evelyne Rey,¹ Louis-Philippe Boulet²

¹Departments of Medicine and Obstetrics and Gynaecology, Faculty of Medicine, University of Montreal, CHU Ste-Justine, 3175 Côte-Ste-Catherine, Montreal, QC, Canada H3T 1C5

²Institut de cardiologie et de pneumologie de l'Université Laval, Hôpital Laval, 2725 Chemin Sainte-Foy, Québec City, QC, Canada G1V 4G5

Correspondence to: E Rey
evelyne_rey@ssss.gouv.qc.ca

BMJ 2007;334:582-5
doi: 10.1136/bmj.39112.717674.BE

Doctors often encounter pregnant patients who have asthma but have limited knowledge of asthma and its optimal treatment (see Scenario box). After treating an acute episode in a presenting patient, the doctor should advise her about asthma, its impact on pregnancy, and the best way to manage her asthma.

How common is asthma in pregnancy?

Asthma is a serious health problem worldwide, and its prevalence has increased in the past two decades.^{w1} With 3.4%-12.4% of pregnant women having asthma, it is the most common chronic condition in pregnancy.^{w2 w3} The many national and international guidelines on the management of asthma apply also to pregnant women.^{1 2 w4-w6}

Does pregnancy affect asthma?

Some historical cohort and prospective studies have found that during pregnancy the severity of asthma remains stable in a third of women, worsens in another third, and improves in the remaining third.^{w7 w8} Two prospective studies showed, however, that during

Box 1 | Physiological factors affecting asthma in pregnancy

- Increase in free cortisol levels may protect against inflammatory triggers
- Increase in bronchodilating substances (such as progesterone) may improve airway responsiveness
- Increase in bronchoconstricting substances (such as prostaglandin F₂ α) may promote airway constriction
- Placental 11 β hydroxysteroid dehydrogenase type 2 decreased activity is associated with an increase in placental cortisol concentration and low birth weight
- Placental gene expression of inflammatory cytokines may promote low birth weight
- Modification of cell mediated immunity may influence maternal response to infection and inflammation

pregnancy the condition is more likely to deteriorate in women with severe asthma (52%-65%) than in those with mild asthma (8%-13%).^{3 4} Exacerbations are most likely to occur between 24 and 36 weeks of pregnancy.^{3 w9} In a prospective study Murphy et al observed that respiratory viral infections were the most common precipitants of exacerbations (34%), followed by non-adherence to inhaled corticosteroid medication (29%).³ Another small prospective study showed that among pregnant women, those with severe asthma were more likely to have respiratory or urinary tract infections (69%) than those with mild asthma (31%) or those without asthma (5%).^{w10} Thus, women with asthma need to be closely followed during pregnancy, regardless of the severity of the disease. Box 1 outlines the physiological factors affecting asthma in pregnancy.

Does asthma affect pregnancy?

Few data exist on how asthma control before pregnancy affects pregnancy outcomes. In a nested case-control study including 1808 asthmatic women, Martel et al observed that markers of poor asthma control and severity before pregnancy were associated with an increased risk of hypertension during pregnancy.^{w11}

Conflicting data exist on the effects of asthma on pregnancy outcomes, due mainly to different study designs, different severity and management of asthma, and inadequate control for confounders. Adverse associations, for example, were more common in historical studies than in prospective studies with active

SCENARIO

A 30 year old woman presented to the emergency department complaining of breathlessness. She was 22 weeks pregnant, and her pregnancy had been complicated by nausea and gastric pain. She had had asthma since childhood, had visited the emergency room at least once a year in the previous three years, but had not been followed up regularly. She had used inhaled budesonide irregularly in the past and stopped this medication when she became pregnant. She had been having flu-like symptoms in the previous week and used inhaled salbutamol three or four times a day with partial relief.

On examination, we observed a low grade temperature, normal blood pressure, tachycardia (120 beats/min), tachypnoea (28 breaths/min), expiratory wheezes on chest auscultation, and a normal fetal heart rate. Her oxygen saturation was 96% and spirometry showed a forced expiratory volume in one second of 42% predicted.

The initial treatment was inhaled salbutamol, oxygen at 5 l/min, and oral prednisone 40 mg. She improved sufficiently within 24 hours to be discharged with prednisone for a week, in addition to regular budesonide and (on demand) terbutaline, medication which was used until delivery. She was referred to an asthma educator and regular medical follow-up appointments were scheduled.

This is the first in a series of occasional articles about how to manage a pre-existing medical condition during pregnancy. If you would like to suggest a topic for this series please email Kirsten Patrick (kpatrik@bmj.com)

management.⁵ The many studies on the effects of asthma on pregnancy outcomes have been analysed in detail recently.^{5 6 7 w12}

Low birth weight or intrauterine growth restriction have been reported in historical studies in pregnant women with asthma^{6 w7} but not in large prospective studies.^{8 w9 w13} However, two recent, large, well conducted prospective studies did report that low birth weight was more common in women who specifically had daily symptoms of moderate asthma⁹ or a low expiratory flow, than in women without asthma.^{w14}

A systematic review found an increase in low birth weight in 1453 asthmatic women (four studies) not using inhaled corticosteroids (relative risk 1.55; 95% confidence interval 1.28 to 1.87).⁵ Another systematic review, which included three studies and 934 asthmatic women, found that asthma exacerbations during pregnancy significantly increased the risk of low birth weight compared with non-asthmatic women (2.54; 1.52 to 4.25) and women without exacerbations (2.27; 1.29 to 3.97).⁶

A large prospective study of 1739 asthmatic women found no increase in preterm delivery,⁸ a finding confirmed by a meta-analysis on the impact of asthma exacerbations (four studies, 1438 women).⁶ However, Schatz et al reported an association between prematurity and low respiratory flow in a large prospective study.^{w14}

Historical studies have reported an association between asthma and hypertension during pregnancy.⁵ Two large, multicentre, prospective, well conducted studies reported an increase in gestational hypertension in women with daily asthma symptoms⁹ or with a low respiratory flow.^{w14} A systematic review that included two studies and 966 asthmatic women found that asthma exacerbations were not a risk factor for pre-eclampsia (1.37; 0.65 to 2.92).⁶ Historical and prospective studies have reported a higher frequency of caesarean section in asthmatic compared with non-asthmatic women.^{8 w7 w9}

All these data suggest that asthma severity and suboptimal control are associated with adverse pregnancy outcomes. Box 2 suggests special management approaches for pregnant women with asthma, and box 3 outlines the main differential diagnoses in pregnant women with dyspnoea.

Box 2 | Special considerations in pregnant women with asthma

- Ensure optimal asthma control throughout pregnancy
- Manage asthma exacerbations aggressively
- Avoid delay in diagnosis and treatment
- Assess medication needs and response to therapy frequently
- Ensure adequate patient education and acquisition of self management skills
- Treat rhinitis, gastric reflux, and other comorbidities adequately
- Encourage smoking cessation
- Assess pulmonary function (expiratory flow) with spirometry at least monthly
- Offer a multidisciplinary team approach
- Do not give flu vaccination until after 12 weeks of pregnancy
- Be aware of the risk of pre-eclampsia and intrauterine growth retardation

Box 3 | Main differential diagnoses in pregnant women with dyspnoea

- *Asthma*—Acute or progressive dyspnoea with wheezing and cough, more often with a history of asthma and precipitating factors; diagnosis confirmed by pulmonary function tests
- *Physiological dyspnoea of pregnancy*—Hyperventilation due mainly to increased progesterone; may occur early in pregnancy and does not interfere with daily activities
- *Pulmonary embolism*—Acute respiratory distress or gradually progressive dyspnoea with or without tachycardia, cough, chest pain, haemoptysis, or signs of deep venous thrombosis; diagnosis established by scintigraphic ventilation perfusion scan, computed tomographic angiography, or pulmonary angiography
- *Pulmonary oedema*—Acute or progressive respiratory distress in the presence of heart disease, hypertension, embolic disease, tocolytic therapy, aggressive fluid replacement, or sepsis; diagnosis confirmed by chest radiography
- *Peripartum cardiomyopathy*—Dyspnoea caused by dilated cardiomyopathy occurring during the final month of pregnancy to six months after delivery; signs and symptoms of heart failure confirmed by echocardiographic evaluation
- *Amniotic fluid embolism*—Acute respiratory distress occurring more often during the evacuation of the uterus and which may be complicated by hypotension, seizure, disseminated intravascular coagulation, and cardiac arrest

Management of asthma in pregnancy

The general principles of the management and treatment of asthma are the same in pregnant women as in non-pregnant women and in men.^{1 2 w4-w6} Some precautions should be taken, however, in managing asthma exacerbation in pregnancy (box 4). Reports from a large prospective study including 1739 asthmatic women indicated that adequate management of asthma in pregnancy decreases adverse maternal and fetal morbidity.^{4 8} The intensity of antenatal fetal surveillance (fetal ultrasonography and non-stress test) should be based on the severity of asthma, the risk of intrauterine growth retardation, and pre-eclampsia.

Education

Pregnancy is a good time to review the patient's basic understanding of asthma and its management, including trigger avoidance, asthma control, and adequate use of devices, medication, and personal action plans. Women and doctors should be vigilant for the presence of environmental factors such as allergens that may need to be tackled during pregnancy. Useful information is available on the websites of national pulmonary societies and international organisations, and patients can be referred to these if they seek additional information.² Furthermore, whenever possible, the educational intervention that started in the doctor's surgery should be continued by an asthma educator.

Box 4 | Management of acute asthma in pregnancy

- Intervene rapidly
- Closely monitor the woman and assess fetal wellbeing continuously
- Maintain oxygen saturation >95%
- Avoid PaCO₂ >40 mm Hg
- Place woman in a left lateral position
- Provide ample hydration with intravenous fluid (isotonic saline 125 ml/h) if drinking is impossible
- Avoid hypotension with adequate position, hydration, and treatment
- Use adrenaline (epinephrine) only in the context of an anaphylactic reaction
- Consider intubation earlier than usual and call an expert if intubation is required as it can be more difficult in pregnant women owing to the oedema of the oropharyngeal mucosa

Pharmacological treatment in pregnancy

Many mothers and their doctors are concerned about the potential effects of asthma drugs—on their babies as well as on the women themselves. In a recent large cohort study, Enriquez et al reported that asthmatic women decreased their use of inhaled corticosteroids by 23%, of short acting β_2 agonists by 13%, and of additional oral corticosteroids for exacerbations by 54% when becoming pregnant.^{w15} Cydulka et al found that in emergency departments doctors were less likely to prescribe corticosteroids both initially and on discharge to pregnant women than to non-pregnant women (initially, 44% v 66%; on discharge, 38% v 64%).^{w16}

It is safer, however, to take asthma drugs in pregnancy than to leave asthma uncontrolled as large prospective studies have shown that adverse perinatal outcomes are associated with uncontrolled asthma and reduced expiratory flow.^{9 w14} Moreover, prospective studies, case-control studies, and systematic reviews have shown that inhaled corticosteroids, theophylline, and short acting β_2 agonists do not increase the risk of fetal congenital malformations, pre-eclampsia, preterm delivery, or low birth weight.^{10 w11 w17 w18} Therefore, treatment for achieving and maintaining adequate asthma control should be prescribed and compliance regularly assessed.

Although pregnancy modifies the absorption rate and pharmacokinetics of some medications, the dose or regimen of asthma medications do not usually need to be changed in pregnancy. Case-control studies have found that systemic decongestants used in the first trimester are associated with small increases in risk of fetal gastrochisis, intestinal atresia, and hemifacial microsomia.^{w19}

Epidemiological studies have shown that oral corticosteroids in the first trimester are associated with an increased risk of fetal cleft lip or palate.^{w20} However, as the increased incidence is small (rising from 0.1% to 0.3%) compared with the benefits of using such medication to regain asthma control quickly, the practitioner should not refrain from using oral corticosteroids in severe asthma and life threatening situations.

Large prospective and case-control studies have found that oral corticosteroids are associated with preterm delivery and pre-eclampsia.^{19 w11 w21} Importantly, prednisone is inactivated at 90% by the placenta, which limits fetal exposure to the active drug and the risk of fetal withdrawal.^{w22}

Inhaled corticosteroids remain the cornerstone of treatment for persistent asthma, regardless of its severity. They are safe in pregnancy, and large prospective studies, case-control studies, and systematic reviews have shown that they are not associated with fetal malformations or perinatal morbidity.^{5 10 w11 w17 w18} Large prospective studies and randomised trials have also shown that inhaled corticosteroids prevent asthma exacerbations in pregnancy.^{10 w9 w23 w24} Most studies on inhaled corticosteroids in pregnancy have been conducted with budesonide, but the corticosteroid that was used successfully before pregnancy should be continued into childbirth.^{w25}

Prospective, observational, and case-control studies have shown that cromolyn sodium and short acting β_2 agonists are safe during pregnancy.^{9 10 w11 w21 w26}

Few data exist on long acting β_2 agonists used alone or in combination with inhaled corticosteroids. Salmeterol and formoterol at high doses are associated with fetal malformations in animals, but these drugs did not cause fetal malformations, preterm delivery, or low birth weight in the limited number of women using them in prospective studies.^{9 w27 w28} As is the case outside pregnancy, long acting β_2 agonists should always be used together with an inhaled corticosteroid, ideally in a combination product.^{w29}

Data are scarce on the safety of leukotriene modifiers in pregnancy. No fetal malformation or adverse outcomes in pregnancy were seen in nine women exposed to a leukotriene modifier in the prospective study by Bracken et al⁹ or in 176 women exposed to montelukast (145 in the first trimester) according to the manufacturer.^{w30}

Animal studies show no teratogenicity with montelukast or zafirlukast but do show such risk with zileuton (not licensed in the United Kingdom).^{w22} In the absence of strong data on the safety of these drugs it seems reasonable to replace them with an inhaled corticosteroid at the start of pregnancy or with a long acting β_2 agonist (if this is used as an “add on” therapy).

Theophylline has been reported to be safe in human pregnancy at recommended doses.^{1 w21 w24} Serum theophylline levels should be monitored because drug metabolism changes in pregnancy. Theophylline is rarely used now in asthma, however, and it remains a last treatment option in moderate or severe asthma.

Does asthma affect labour and delivery?

Labour and delivery are not usually affected by asthma, but prospective studies have shown that 10%-20% of women experience an exacerbation during labour.^{w8 w9} The drugs should be continued and adjusted according to need during this period. Box 5 outlines procedures and medications for women with asthma during labour.

Box 5 | Procedures and medications during labour

- Continue medications and give short acting β_2 agonists or corticosteroids, or both, if asthma is not well controlled
- Provide ample hydration with intravenous fluid
- Evaluate pulmonary status and oxygen saturation on admission, and later as needed
- Favour lumbar epidural analgesia to provide adequate pain relief (which decreases bronchospasm) and to reduce oxygen consumption and minute ventilation
- Give stress dose of corticosteroids (such as 50-75 mg a day of hydrocortisone equivalent for one to two days^{w31}) if systemic corticosteroids have been taken within previous months
- Avoid bronchoconstrictor agents for management of abortion or labour (such as prostaglandin F2 α) or for postpartum haemorrhage (such as ergonovine, methylergonovine (neither is licensed in the UK), and carboprost)

Does asthma affect postpartum period and breast feeding?

The postpartum period is not associated with an increased rate of asthma exacerbations. In women who experienced a change of severity during pregnancy, the severity reverts to pre-pregnancy level within three months after the birth.^{w8} Few data are available on the safety of asthma drugs in breastfed neonates. Most drugs are considered to be safe, but irritability or sleepiness have been reported in the breastfed neonates of women taking theophylline and antihistamines.^{w22 w32} Non-steroidal anti-inflammatory drugs should be avoided in women intolerant to aspirin.

Conclusions

Asthma may be influenced by pregnancy, but the outcome and prognosis of most asthmatic mothers and their newborn infants are usually favourable, particularly if the women's asthma is well controlled in pregnancy. Exacerbations should be prevented by optimal asthma management, and if they occur they should be treated aggressively. Women's drug treatment needs should be regularly assessed in the light of asthma control criteria, including measures of expiratory flow.

Contributors: Both authors performed the literature search. ER wrote the first version of the manuscript, which was revised many times by both authors. ER is the guarantor of the paper.

Competing interests: None declared.

Provenance: Commissioned and peer reviewed.

- 1 National Asthma Education and Prevention Program Working Group. Managing asthma during pregnancy: recommendations for pharmacologic treatment—2004 update. Expert panel report. *J Allergy Clin Immunol* 2005;115:34-46.
- 2 Global Initiative for Asthma (www.ginasthma.com)
- 3 Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol* 2005;106:1046-54.
- 4 Schatz M, Dombrowski MP, Wise R, Thom EA, Landon M, Mabie W, et al. Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol* 2003;112:283-8.
- 5 Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and treatment implications. *Eur Respir J* 2005;25:731-50.
- 6 Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006;61:169-76.
- 7 Gluck JC, Gluck PA. Asthma controller therapy during pregnancy. *Am J Obstet Gynecol* 2005;192:369-80.
- 8 Dombrowski MP, Schatz M, Wise R, Momirova V, Landon M, Mabie W, et al. Asthma during pregnancy. *Obstet Gynecol* 2004;103:5-12.
- 9 Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. *Obstet Gynecol* 2003;102:739-52.
- 10 Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. The relationship of asthma medication use to perinatal outcomes. *J Allergy Clin Immunol* 2004;113:1040-5.

Unsafe driving

Early in my medical career my aged car—which I had bought with my first month's wages—had broken down, and the hospital arranged to pay a minicab driver to take me to another hospital.

The minicab driver, who seemed to be in his late 30s, made an illegal right turn to speed the wrong way up a short one-way street. I asked him if he was in a rush, because I was not. He told me that he was: this was his last job of the day, and he wanted to get to his general practitioner as he had high blood pressure, and it needed to be checked.

I wondered whether to advise him that if he cut his speed and avoided driving the wrong way up a one-way street, then his high blood pressure might improve. I doubted whether his general practitioner would know as much about this man's driving as he or she did about his blood pressure.

I remained silent until we completed our journey, keen to keep the driver's concentration on driving rather than speaking. I was pleased to reach my destination without anyone getting injured. I told a senior colleague of my concern that any patients or staff transported by this cab driver could be at risk, but her reply was that no

one would do anything about it because of the cost of the contract with the taxi company. I did not, therefore, formally report this, but nowadays I would.

I am obliged to breach confidentiality under General Medical Council guidelines several times a year. I have to inform the medical adviser at the Driver and Vehicle Licensing Agency that a patient with dementia, who is incapable of understanding advice not to drive and insists on continuing to do so, is unsafe to drive. The result is usually revocation of licence, a distressed patient, relieved family, and arguably maintained public safety.

Many such patients tell me that they are safer drivers than younger drivers who drive badly. I sometimes agree with them that they may be right but add that I still must follow GMC guidelines. I find it strange that I am obliged to breach confidentiality for this small minority of patients, when I do not report the far more numerous instances of unsafe driving I see outside work, by young people who are not my patients.

Peter Simmons consultant psychiatrist, Queen Elizabeth II Hospital, Welwyn Garden City
PSimmons@doctors.org.uk