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Current Obstetrics & Gynaecology (2004) **14**, 175–182

Current
OBSTETRICS &
GYNAECOLOGY

www.elsevier.com/cuog

Respiratory disease in pregnancy

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KEYWORDS
Respiratory tract diseases;
Pregnancy complications;
Asthma;
Respiratory tract infections

Summary A variety of respiratory complications can be encountered in pregnancy. An understanding of the pathophysiology of pregnancy is important in the management of such complications. Despite the changes in immunity, the incidence of respiratory infections is not higher in pregnancy. Asthma is the most common preexisting medical disorder encountered in pregnancy, and its prevalence in women of childbearing age is increasing. There is a slight increase in the risk to the pregnancy, but suboptimal therapy is the most common reason for poor control. X-rays should be obtained whenever clinically indicated, and most drugs used in the management of asthma have a long track record of safety. For women with poor control in pregnancy, there should be good liaison between the respiratory physician and the obstetrician. Tuberculosis is increasingly important and may complicate human immunodeficiency virus infection. First-line antituberculous drugs can safely be administered in pregnancy and lactation.

Pregnancy changes in the respiratory system

Normal pregnancy is associated with an increase in ventilation, mainly due to deeper but not more frequent breathing. These changes lead to an increase in basal oxygen consumption. The majority of women are more aware of their breathing, which may lead to the common complaint of shortness of breath. This is most common in the third trimester and may lead to diagnostic confusion. In late pregnancy, the diaphragmatic elevation caused by the enlarging uterus leads to a decrease in functional residual capacity (FRC), but diaphragm excursion is unaffected so vital capacity is unchanged. Pregnancy-induced physiological changes that occur in the respiratory system are summarized in Table 1.

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Asthma

Asthma is the most common preexisting medical disorder encountered in pregnancy, and its prevalence in women of childbearing age is increasing. The biggest danger to the mother and her fetus comes from poorly controlled or undertreated disease. Management during pregnancy should include education regarding inhaler use and reassurance about the safety of medications used to control asthma.

The effect of pregnancy on asthma

The natural history of asthma in pregnancy is very variable. Literature addressing the effect of pregnancy on asthma is conflicting, with no consistent trend to improvement or worsening of disease severity. Some North American studies suggest that between one in five and one in nine women with asthma will have at least one admission to the

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doi:10.1016/j.curobgyn.2004.02.002

Table 1 Pregnancy-induced physiological changes in the respiratory system.

Increased in pregnancy	Unchanged in pregnancy	Decreased in pregnancy
Basal metabolic rate	Respiratory rate	Partial pressure of carbon dioxide
Oxygen consumption	Forced expiratory volume in 1 s	Residual lung volume
PH	Peak expiratory flow rate	
Tidal volume	Vital capacity	

emergency department, and of these, 62% will require hospitalization. The course of asthma in pregnancy in an individual woman is largely unpredictable. Women commencing pregnancy with severe or poorly controlled disease will experience worsening of symptoms, particularly in the third trimester, compared with those with mild disease. There is some evidence that the course of the disease is similar in successive pregnancies. Many asthmatics experience worsening of their symptoms during pregnancy because they stop or reduce medication due to fears (either their own or their medical advisers') about its safety. The current UK guidelines recommend prepregnancy counselling to women with asthma regarding the importance and safety of continuing their asthma medication during pregnancy to ensure good control.

The effect of asthma on pregnancy

During pregnancy, there is an increased incidence of complications, both maternal and fetal. These complications, often serious, happen nearly exclusively in patients with severe and/or poorly controlled asthma. In a recent study, the most common maternal complications were meconium-stained amniotic fluid, preterm labour or delivery, oligohydramnios and pregnancy-induced hypertension. There was some evidence of a modest association between maternal asthma and risk of preterm premature rupture of membranes.

The most common neonatal complications were meconium staining, preterm infant and intrauterine growth restriction (IUGR). Women who required systemic steroids were more likely to have oligohydramnios, IUGR, meconium staining or pregnancy-induced hypertension.

Pregnancy should be seen as an opportunity to optimize asthma control to prevent acute deterioration.

Management of asthma in pregnancy

The successful management of asthma during pregnancy requires a co-operative multidisciplinary approach between obstetricians and midwives, the physician and nurse specialists managing the asthma, and the woman herself. It includes: objective assessment of pulmonary function and fetal well being (home peak flow monitoring and personalized self-management plans are successful in the well-motivated pregnant asthmatic), avoidance of asthma triggers, pharmacological therapy and patient education.

Drug treatment of asthma in pregnancy is similar to treatment in non-pregnant women. All the drugs commonly used to treat asthma, including short- and long-acting β2 agonists, inhaled corticosteroids and methyl xanthines, are safe in pregnancy. Fluticasone may be used for those requiring high doses of inhaled steroids.

Oral corticosteroids

As systemic corticosteroids have serious and well-known side-effects when given frequently or in high doses for prolonged periods, women and their doctors are reluctant to use steroids in pregnancy. Most of this concern is misplaced, and steroids should be used to treat asthma in pregnancy in the same way and for the same reasons as in the non-pregnant state. About 90% of prednisolone is metabolized by the placenta and therefore only small quantities of the active drug reach the fetus. Several studies suggest no increased risk of abortion, stillbirth, congenital malformations, adverse fetal effects or neonatal death attributable to treating the mother with steroids. The maternal adverse effects from steroid therapy in pregnancy include increased risk of infections, reduced glucose tolerance and increased gestational diabetes. The development of hyperglycaemia (treatable with insulin) is not an indication to discontinue or decrease the dose of oral steroids, the requirement for which must be determined by the asthma. The rare, but important, psychiatric side-effects of oral glucocorticoids (with prednisolone $\geqslant$30 mg) should be remembered, and all women who have been commenced on steroids should be reviewed within 1 week.

Leukotriene receptor antagonists

Data regarding the safety of leukotriene receptor antagonists in pregnancy are extremely limited. These agents should not be commenced in a pregnant asthmatic. They may, however, be continued in women achieving asthma control that is not achieved with any other medications.

Management of acute asthma attack

There is evidence that pregnant women presenting with an acute asthmatic attack are less likely than their non-pregnant counterparts to receive appropriate treatment with steroids. Hence, they are more likely to experience ongoing exacerbations.

In the last two Confidential Enquiries into Maternal Deaths in the UK (1994–1999), there were eight indirect maternal deaths from asthma. Drug therapy should be given as for a non-pregnant patient with asthma, including repeat doses of inhaled β2 agonists and early administration of oral steroids. The treatment aim is to maintain the partial pressure of oxygen greater than 60 mmHg and oxygen saturation above 95%. In severe cases, intravenous treatment with magnesium sulphate, β2 agonists or aminophylline can be used as indicated. Continuous fetal assessment should be performed when asthma is uncontrolled or severe, or when the initial assessment is non-reassuring. Acute severe asthma in pregnancy should be considered as an emergency and should be treated vigorously in hospital. Provided abdominal shielding is used, a chest X-ray results in minimal exposure of the fetus to ionizing radiation, and if clinically indicated, this investigation must never be withheld just because the patient is pregnant.

For women with poor control in pregnancy, there should be good liaison between the respiratory physician and the obstetrician.

Management of asthma during labour and delivery

Acute attacks of asthma during labour and delivery are extremely rare, and women should be reassured accordingly. Regularly scheduled medications should be continued during labour. Those on oral steroids ($>$7.5 mg prednisolone) more than 2 weeks preceding labour should receive parenteral steroids (hydrocortisone 100 mg 6–8 hourly) during labour and until they are able to restart their oral medication. Prostaglandin E2, used to induce labour, is a bronchodilator and is safe. Prostaglandin F2α, indicated for severe postpartum haemorrhage, should be used with extreme caution as it may cause bronchospasm.

Women with asthma may safely use all forms of pain relief in labour, including epidural analgesia and Entonox. Non-histamine-releasing narcotics, such as fentanyl, are preferred to the other opiates. If anaesthesia is required, women should be encouraged to have an epidural rather than general anaesthesia because of the increased risk of severe bronchospasm, chest infection and associated atelectasis. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain relief following caesarean section. Women with asthma should be asked about any known aspirin or NSAID sensitivity prior to the use of these drugs.

Breastfeeding

Women with asthma should be encouraged to breastfeed. The risk of atopic disease developing in the child of an asthmatic woman is about one in 10, or one in three if both parents are atopic. Breastfeeding may reduce this risk. All inhaled preparations, oral steroids and methylxanthines are safe when breastfeeding.

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal-recessive disorder arising from a defect on chromosome 7 in the region coding for the CF transmembrane regulator protein. Abnormal quantity or function of this protein results in disturbed ion and water transport across cells of many glands. This is responsible for excessively thick secretions that can cause obstruction, organ damage and loss of function. The carrier frequency is 1:25 in Caucasians, with an estimated prevalence of one in 2500 livebirths.

The clinical picture is dominated by early persistent and recurrent respiratory infection despite attempts at prevention and aggressive treatment. However, chronic infection with progressive lung damage is inevitable, leading to respiratory failure. The other feature is pancreatic insufficiency from obstruction, which necessitates lifelong supplementation with pancreatic enzymes. Malabsorption and poor growth are common. Other problems include biliary cirrhosis from obstruction to biliary ductules, pancreatic endocrine dysfunction leading to glucose intolerance and CF-related diabetes, and osteoporosis. With the development of specialized centres and various other interventions, the median survival has steadily increased

from early teens in the 1960s to the fourth decade and beyond at present. The feasibility of lung transplantation has helped improve survival. Although fertility is uniformly affected in male CF sufferers, it is relatively unaffected in females.

Effect of CF on pregnancy

Many hundreds of CF pregnancies have now been reported. A Scandinavian study reporting on 80 pregnancies in 162 women with CF found that 46 (75%) of 61 women considering pregnancy could achieve it, although assisted reproduction was required in 15%. A large proportion of those who achieved pregnancy continued it, with 10% choosing termination of pregnancy as an option. This indicates that these women were highly motivated.

Healthy women with CF can have successful pregnancies without detriment to their condition. This hitherto meant women without pancreatic insufficiency. However, with enzyme supplementation and proper diet management, increasing numbers of women with pancreatic insufficiency are entering pregnancy in a relatively 'healthy' state. To achieve adequate weight gain in pregnancy, many will require oral, nasogastric, gastrostomy or parenteral supplementation. Rates of preterm birth are high, particularly with low maternal weights, but perinatal mortality is surprisingly low. Sometimes preterm delivery may be medically indicated in unwell women. Therapeutic termination of pregnancy may be required in very sick women, underscoring the need for effective contraception in those not wishing to get pregnant. Should the condition be complicated by CF-related diabetes, the pregnancy outcome is adversely affected. Although the outcome is consistently improving with time, it still remains inferior compared with those without CF-related diabetes. Pregnancy in lung transplant recipients with CF has been reported. Although the data are relatively limited, they seem to agree with the experience with other organ transplants. Rejection of the transplant is more common in the first 2 years, so pregnancy should ideally not be embarked upon during this time. A pregnancy undertaken more than 2 years after transplant is expected to be associated with little risk of transplant rejection, organ failure or fetal anomalies.

Severely deranged liver function constitutes a contra-indication to pregnancy. However, mild elevation of liver enzymes and/or abnormal liver ultrasound scans are relatively common, and do not have a major impact on the outcome. Pulmonary hypertension and right heart failure are the other contra-indications to pregnancy in women with CF.

CF is an autosomally transmitted disease, and genetic counselling should be offered to those women with CF considering pregnancy. If the partner is not a carrier of any known mutation, the risk of CF to the offspring is extremely small. However, the baby will be a carrier of the CF gene mutation.

Effect of pregnancy on CF

The two large studies looking at the effect of pregnancy on CF are contradictory. A North American study suggested no deleterious effects of pregnancy on CF or worsening of lung function. In contrast, a UK study suggested that those with poor lung function delivered earlier, and those delivering earlier lost more pulmonary function compared with non-pregnant CF controls matched by severity.

Pneumonia in pregnancy

Pregnancy is considered to be a state of relative immunosuppression. Studies have shown that maternal cell-mediated immunity is depressed during pregnancy. In the second and third trimesters, maternal lymphocytes show a decreased proliferative response to both soluble antigens and allogenic lymphocytes. A reduction in T helper cells results in a lower helper/suppressor ratio, causing decreased antibody production. Polymorphonuclear leukocytes show a reduction in the chemotactic response during pregnancy.

Despite this immunosuppression, the prevalence of pneumonia in pregnancy is no different compared with the non-pregnant individual. However, complications associated with pneumonia may be more common. The most common causes of pneumonia are bacterial, viral and aspiration.

The common organisms causing pneumonia in pregnancy are summarized in Table 2, and are similar to those found in non-pregnant women.

Bacterial

Streptococcus pneumoniae is the most common pathogen, and is identified in 30–50% of all pneumonias. Mycoplasma is identified in about 10% of antepartum pneumonias. Mortality from mycoplasma is rare, and recovery generally occurs 10–14 days after the onset of symptoms. Although legionella is encountered in 5% of women, the mortality rate can be as high as 20%.

Table 2 Common causative organisms of pneumonia.

Bacterial	*Sterptococcus pneumoniae* *Haemophilus influenzae* *Klebsiella pneumoniae* *Staphylococcus aureus* *Mycobacterium tuberculosis*
Atypical	*Mycoplasma hominis*
Viral	Influenza Type A Varicella Rubeola (measles)
HIV associated	*Pneumocystis carinii* Coccidioidomycosis Cryptococcus

Viral

Type A influenza is a frequent cause of viral pneumonia, and is associated with more risks in pregnancy than in the non-pregnant state. Varicella pneumonia may occur in up to 20% of pregnant women with varicella infection. Pneumonia develops 3–6 days after vesicular eruption. The chest X-ray typically shows a diffuse nodular pattern. If varicella pneumonia is suspected in a pregnant woman, it is prudent to admit her to hospital for observation and to treat with Acyclovir. Maternal infection with measles (Rubeola) should also be closely observed for developments of complications including pneumonia. Antibiotic treatment is recommended in the event of super-added bacterial infection.

Human immunodeficiency virus

Similar to the non-pregnant state, pneumocystis (PCP) and tuberculosis are the most frequent pulmonary complications in pregnant women infected with human immunodeficiency virus (HIV). Pregnancy does not appreciably alter the work-up and management of HIV-associated pneumonia except for issues related to potential fetal effects. PCP has a more aggressive course during pregnancy, with increased morbidity and mortality. Maternal and fetal outcomes remain dismal. Treatment with sulphamethoxazole-trimethoprim, compared with other therapies, may result in an improved outcome. Withholding appropriate PCP prophylaxis may have an adverse effect on maternal and fetal outcomes. More than 80% of women with acquired immunodeficiency syndrome (AIDS) are of reproductive age, and PCP is the most common cause of AIDS-related death in pregnant women in the USA. Among 22 cases recently reviewed in the Division of Infectious Diseases, Brooklyn, New York, USA, the mortality rate was 50% (11 of 22 patients), which is higher than that usually reported for HIV-infected individuals with PCP. Respiratory failure developed in 13 patients (59%), and mechanical ventilation was therefore required; the survival rate in patients requiring mechanical ventilation was 31%. Maternal and fetal outcomes were better in cases of PCP during the third trimester of pregnancy.

Coccidioidomycosis carries an increased risk of dissemination and higher mortality in pregnancy. If dissemination occurs, treatment with Amphotericin-B is indicated. Amphotericin has been widely used without evidence of teratogenicity. The use of fluconazole as a first-line therapy is not recommended due to the risk of fetal malformations. Bacterial pneumonia is more frequent in HIV-positive individuals than in seronegative controls, and the risk is highest among those with CD4 lymphocyte counts below 200/mm^3 and among injection-drug users. There is evidence of a change in the causative organisms of pneumonia in pregnancy. *Pseudomonas aeruginosa* is becoming a common cause of both community acquired and nosocomial bacterial pneumonia in hospitalized patients with HIV, especially in those with low leukocyte and CD4+ lymphocyte counts. Although the incidence of nosocomial bacterial pneumonia, as well of other opportunistic infections, decreased considerably with the advent of highly active antiretroviral therapy, it still represents an important cause of mortality.

The global HIV epidemic is increasing the tuberculosis all-cause mortality. As well as affecting the individuals, increased caseloads due to HIV may also contribute to increased mortality by reducing the health system's ability to provide adequate care.

Terminating the pregnancy is not usually beneficial to the maternal outcome unless improving the respiratory capacity may improve the condition. In addition, there are ethical dilemmas of terminating a pregnancy without maternal consent if the mother is unconscious.

Aspiration pneumonia

Pregnant women are at an increased risk of aspiration due to increased intra-abdominal

pressure, delayed gastric emptying time and decreased gastro-oesophageal sphincter tone. Prevention is the mainstay of treatment. Chemical pneumonitis usually results due to aspiration of acidic gastric contents. Antibiotics are used if bacterial infection is suspected. The use of steroids is controversial and cannot be recommended.

Granulomatous diseases

Tuberculosis

Tuberculosis (TB) is becoming an important infection, particularly with the increasing prevalence of HIV seropositivity. Treatment regimens consist of an initial (intensive) phase lasting 2 months. During the initial phase, normally consisting of isoniazid, rifampicin, pyrazinamide and ethambutol, the tubercle bacilli are killed rapidly. This is followed by a continuation phase, usually lasting 4 or 6 months. Patients negative for HIV, with smear-negative pulmonary or extrapulmonary TB that is fully drug susceptible, have little risk of selecting resistant bacilli because their lesions generally harbour fewer bacilli. However, since initial resistance to isoniazid is common in many areas, and HIV testing of tuberculosis patients is not practiced routinely, it is now recommended that ethambutol be included as a fourth drug during the initial phase of treatment for most patients with smear-negative pulmonary and extrapulmonary TB. Ethambutol may be omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli, and young children with primary TB. Breastfeeding is safe while the mother is receiving antituberculous therapy.

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology. Sarcoidosis complicates approximately one in 2000 pregnancies. Most often, patients are asymptomatic, but chest symptoms may occur. Erythema nodosum, arthropathy, fever, hypercalcaemia and central nervous system (CNS) involvement may be the presenting symptoms. It may be associated with an abnormal chest X-ray (Hilar lymphadenopathy) in 30% or erythema nodosum with arthralgia in 30%. Serum angiotensin-converting enzyme (ACE) level is used outside pregnancy to monitor disease activity, but is of no use in pregnancy due to the physiological increase in serum ACE levels in pregnancy. Sarcoidosis is usually self-limiting and does not require therapy. There are no risks to the fetus, although placental sarcoid granulomas have been reported. Therapy may be indicated in the event of CNS symptoms or impairment of respiratory function. Systemic steroids are useful for improvement of the disease. If the patient is already on steroids, they should be continued during the pregnancy. The disease course is often unaltered and sometimes improved in pregnancy. Increase in the steroid dosage after delivery should be considered because post-partum relapse is common. Pregnant women with sarcoidosis should avoid vitamin D as this can precipitate hypercalcaemia.

Acute respiratory distress in pregnancy

Severe acute respiratory syndrome (SARS) was first reported in 2003 in south-east Asia. The causative organism is a new coronavirus that induces symptoms of an atypical pneumonia, but some patients rapidly progress towards adult respiratory distress syndrome. This results in significant hypoxia. The infection may produce a unique set of problems if encountered with pregnancy. It may cause a miscarriage in early pregnancy, IUGR, fetal distress and intra-uterine death.

Maternal oxygen saturation should be maintained above 95%, and mothers should be nursed in the upright position. Women on ventilators are best nursed in the left lateral position in order to maximize uteroplacental blood flow. Cardiotocography with ultrasound assessment of fetal growth and Doppler assessment of blood flow are recommended as fetal monitoring measures. SARS is a very contagious disease and appropriate isolation and infection control protocols are necessary in order to avoid accidental infection of the medical staff. A small group of health professionals should be allocated to look after infected patients, and they should be periodically monitored for signs of early infection. The risk of infection is particularly high at the time of vaginal or operative delivery, and additional precautions such as negative pressure air circulation are recommended. Broad-spectrum antibiotics (Clarithromycin and co-amoxyclav in pregnancy) are recommended to prevent concomitant bacterial infection. Ribavarin, an antiviral agent, is tried in SARS with clinical deterioration. However, it is a known teratogen in animals, so it should be used in pregnancy with extreme caution. Termination of pregnancy should be recommended in women exposed to this agent in early pregnancy. High doses of steroids are also

recommended in sick patients. Bacterial infection as a side-effect of maternal steroid therapy is known, and should be guarded against. SARS virus infection may be particularly severe in pregnancy, and pregnancy termination is an option. Early delivery will reduce the oxygen requirements, and this may be vitally important in critically ill patients. Rapid deterioration, multi-organ failure, fetal compromise and failure to maintain maternal oxygenation, even on ventilator support, along with other obstetric reasons constitute indications for early delivery.

Severe restrictive lung disease

Restrictive ventilatory defects are characterized by a reduction in lung volumes associated with an increase in the forced expiratory volume in 1 s:FVC ratio when lung expansion is limited. This is due to alterations in the lung parenchyma or because of abnormalities in the pleura, chest wall or neuromuscular apparatus.

The majority of pulmonary diseases have their onset after the childbearing years. Chronic respiratory failure due to restrictive lung disorders appears to be well tolerated in pregnancy provided that the vital capacity is greater than 1 l and there is no secondary pulmonary hypertension.

Carbon monoxide poisoning

Carbon monoxide is an odourless, tasteless gas that has a high affinity for and binding to haemoglobin, thus displacing oxygen and impeding its transfer. As fetal haemoglobin has a higher afinity for carbon monoxide, fetal carboxyhaemoglobin levels are 10–15% higher than the mother's. Pregnant women and their fetuses do not tolerate excessive carbon monoxide inhalation. Symptoms usually appear when carboxyhaemoglobin levels are 20–30%. Levels over 50% may be fatal to the mother and, presumably, lower levels are fatal to the fetus. Treatment is supportive with administration of 100% or hyperbaric oxygen.

Practice points

- Offer prepregnancy counselling to women with asthma regarding the importance and safety of continuing their asthma medications during pregnancy to ensure good asthma control.
- Monitor pregnant women with asthma closely so that any change in course can be matched with an appropriate change of treatment.
- For acute asthma, give drug therapy as for the non-pregnant patient. Deliver oxygen immediately to maintain saturation above 95%. Acute asthma in pregnancy should be treated vigorously in hospital.
- β2 agonists, inhaled steroids, and oral or intravenous theophyllines should all be used as normal during pregnancy.
- Use steroid tablets as normal when indicated in pregnancy. Steroids should never be withheld because of pregnancy.
- Do not commence leukotriene antagonists during pregnancy. They may be continued in women who have demonstrated significant improvement in asthma control with these agents prior to pregnancy that has not been achievable with other medications.
- Advise women that acute asthma is rare in labour. If anaesthesia is required, regional block is preferable to general anaesthesia. Prostaglandin E2 is safe in asthmatics, but prostaglandin F2α should be used with extreme caution because of the risk of bronchospasm.
- Encourage women to breastfeed. Use asthma medications as normal during lactation according to the recommendations of the manufacturer.

Further reading

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