

# Respiratory diseases in pregnancy • 1

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## Asthma in pregnancy

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The prevalence of asthma in women of childbearing age is increasing and asthma is the most common pre-existing medical disorder encountered in pregnancy. Management during pregnancy should include reassurance regarding the safety of medications used to control asthma. The biggest danger to the mother and her fetus comes from poorly controlled or under treated disease.

### Changes in respiratory function during pregnancy

Normal pregnancy is associated with a 20% increase in oxygen consumption and a 15% increase in the maternal metabolic rate. This extra demand is achieved via a 40–50% increase in resting minute ventilation, resulting mainly from a rise in tidal volume rather than respiratory rate. This hyperventilation causes the arterial oxygen tension ( $P_{aO_2}$ ) to increase and arterial carbon dioxide tension ( $P_{aCO_2}$ ) to fall, with a compensatory fall in serum bicarbonate to 18–22 mmol/l. A mild respiratory alkalosis is therefore normal in pregnancy (arterial pH 7.44).

Up to 75% of women experience a subjective feeling of breathlessness at some time during pregnancy, possibly due to an increased awareness of the physiological hyperventilation. 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, but diaphragm excursion is unaffected so vital capacity is unchanged. There is no change in peak expiratory flow rate (PEFR) or forced expiratory volume in one second ( $FEV_1$ ) in pregnancy. However, the fall in functional residual capacity (FRC) may exacerbate hypoxaemia because of premature airway closure when acute asthma complicates pregnancy.<sup>1</sup>

### Effect of pregnancy on asthma

Literature addressing the effect of pregnancy on asthma is conflicting, with no consistent trend to improvement or worsening of disease severity. Discrepant results between studies relate to methodology (such as whether studies are retrospective or prospective) and whether the outcome measure is objective or relies on patient recall or reporting of symptoms. Patient selection, effect of medications, and the control population also influence the results of such studies. Two of the largest prospective studies

(totalling almost 600 women), using diaries<sup>2</sup> or medication requirements<sup>3</sup> to assess severity, found similar proportions of women deteriorated (35%, 42%), remained the same (33%, 40%), or improved (28%, 18%). Neither study had matched non-pregnant asthmatic controls.<sup>2,3</sup>

The course of asthma in pregnancy in an individual woman is largely unpredictable.<sup>4</sup> Women with mild disease are unlikely to experience problems, whereas those with severe asthma are at greater risk of deterioration, particularly late in pregnancy.<sup>2,5</sup> Physiological changes during pregnancy that may improve asthma include progesterone mediated bronchodilation and increased serum free cortisol levels. Those that may explain deterioration include increased stress and increased gastro-oesophageal reflux. Many asthmatic patients experience worsening of their symptoms during pregnancy because they stop or reduce medication due to fears (either their own or those of their medical advisers) about its safety.

### Effect of asthma on pregnancy

In most women asthma has no effect upon the outcome of pregnancy. However, severe, poorly controlled asthma may have an adverse effect on fetal outcome as a result of chronic or intermittent maternal hypoxaemia. Some studies have suggested an increase in the risk of premature labour<sup>6–10</sup> or low birth weight,<sup>7,10–12</sup> although two prospective case control studies have not confirmed these findings.<sup>3,13</sup> Similarly, higher rates of pregnancy induced hypertension or pre-eclampsia<sup>3,10,14</sup> and caesarean section<sup>3,9,10,15</sup> have been reported in some studies, but this may be a consequence of increased surveillance of asthmatic pregnancies rather than a result of maternal asthma. Steroid use may act as a confounder.<sup>3,16</sup> There have been reports of increased incidence of transient tachypnoea of the newborn,<sup>17</sup> neonatal hypoglycaemia,<sup>3</sup> neonatal seizures,<sup>18</sup> and admission to the neonatal intensive care unit<sup>9</sup> in the babies of asthmatic women. The magnitude of any effect on adverse perinatal outcome is small and related to the degree of control of the asthma. One retrospective study reported a higher incidence of congenital abnormalities in the children of asthmatic women<sup>10</sup> but this has not been shown to occur in two large prospective studies,<sup>3,13</sup> nor in any of the other studies of asthma in pregnancy<sup>7,16,19</sup> including a recent

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retrospective case control study of 101 pregnancies.<sup>19</sup>

It therefore seems that there may be a slight increased risk to the babies of asthmatic mothers, but this risk is small in actively managed patients and may be minimised by maintaining good control of asthma throughout pregnancy.<sup>20</sup>

### Management of asthma in pregnancy

The successful management of asthma during pregnancy requires a cooperative approach between obstetricians and midwives, the physician, and nurse specialists managing the asthma, and the woman herself. The aims and principles of treatment are the same as in the non-pregnant patient,<sup>21</sup> and asthma should be treated as aggressively in pregnant women as in non-pregnant women.<sup>22</sup> Pregnancy, because of the increased contact with health care professionals, provides an ideal opportunity to optimise asthma management and, in many cases, to diagnose asthma for the first time.<sup>23</sup> Home peak flow monitoring and personalised self-management plans are successful in the well motivated pregnant asthmatic patient. The avoidance of asthma triggers is as important as in the non-pregnant patient.

The drug treatment of asthma in pregnancy is similar to the treatment of asthma in non-pregnant women,<sup>21</sup> with a short acting symptom reliever medication and long term daily medication to address the underlying inflammation.<sup>22</sup> However, it must be remembered that strong and repeated reassurance regarding the importance and safety of regular medication is needed to ensure compliance. All the drugs commonly used to treat asthma, including short and long acting  $\beta_2$  agonists,<sup>24-25</sup> inhaled corticosteroids,<sup>26-27</sup> and methyl xanthines<sup>28</sup> are safe in pregnancy. Fluticasone may be used for those requiring high doses of inhaled steroids.<sup>20</sup> Oral corticosteroids and leukotriene antagonists are considered in more detail below.

#### ORAL CORTICOSTEROIDS

Because 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 outside pregnancy.

Prednisolone is metabolised by the placenta and very little (10%) active drug ever reaches 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.<sup>6-7-16-29</sup> There is a 46 year old report of an increased incidence of cleft palate in the offspring of rabbits treated with cortisone early in gestation,<sup>30</sup> and one recent retrospective study of 1184 cases of cleft lip suggested a possible association with oral corticosteroid treatment.<sup>31</sup> Of the five affected pregnancies in the latter study, two were complicated by multiple congenital abnormalities and in another case

the mother was taking only replacement steroids for Addison's disease. Thus, only two pregnancies (no more than control) were complicated by isolated cleft lip in women taking therapeutic doses of corticosteroids. A larger case-control study of 20 830 cases of congenital abnormality revealed no association between the rate of different congenital abnormalities and corticosteroid treatment in the second and third months of gestation.<sup>32</sup> There have been more recent concerns regarding possible deleterious effects of steroids later in gestation on fetal growth and lung and neuronal development<sup>33</sup> and on hypertension.<sup>34</sup> In addition, as discussed above, the association between asthma and preterm labour may in part be due to corticosteroid therapy<sup>6-7-16</sup> and this association is also described for other medical conditions treated with oral corticosteroids in pregnancy.<sup>35</sup>

The maternal adverse effects from steroid therapy in pregnancy include increased risk of infections and reduced glucose tolerance and increase in gestational diabetes. The blood glucose should be checked regularly and hyperglycaemia should be managed with insulin if necessary. The development of hyperglycaemia 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 should be remembered, and all women who have been started on steroids should be reviewed within 1 week.

An increased risk of pregnancy induced hypertension and pre-eclampsia has been reported in asthmatic women treated with oral corticosteroids.<sup>3-15-16</sup> However, given the maternal and fetal consequences of severe asthma, the use of oral corticosteroids remains clinically indicated in pregnancy.

Thus, inhaled corticosteroids prevent exacerbations of asthma in pregnancy<sup>15</sup> and are the prophylactic treatment of choice.<sup>20</sup> The addition of systemic corticosteroids to control exacerbations of asthma is appropriate, and these must not be withheld if current medications are inadequate.<sup>20</sup>

#### LEUKOTRIENE ANTAGONISTS

At present there is insufficient information to establish whether leukotriene antagonists are safe in pregnancy. Animal studies and post-marketing surveillance by the manufacturer of zafirlukast are encouraging. Current recommendations are that montelukast or zafirlukast could be continued in a patient with resistant asthma who has previously responded well to these drugs.<sup>20</sup>

### Management of acute severe asthma

Acute severe attacks of asthma are dangerous and should be vigorously managed in hospital. In the last confidential enquiry into maternal deaths in the UK<sup>36</sup> there were three deaths from asthma from 1994 to 1996. Treatment is no different from the emergency management of acute severe asthma outside pregnancy. Oxygen, nebulised  $\beta_2$  agonists, nebulised ipratropium, oral or intravenous steroids and, in

severe cases, intravenous aminophylline or intravenous  $\beta_2$  agonists should be used as indicated. Sadly, pregnant women receive appropriate treatment with corticosteroids less commonly than non-pregnant women.<sup>37</sup> A recent US study compared the treatment and outcome of acute asthma in pregnant and non-pregnant women presenting to academic emergency departments. The 51 pregnant women did not differ from the 500 non-pregnant women with respect to duration or severity of asthma symptoms with about 75% of both groups assessed as having severe symptoms and only about 40% of both groups had been using inhaled corticosteroids during the previous month. Both groups received comparable amounts of nebulised  $\beta_2$  agonist treatment in the first hour, but the pregnant women were significantly less likely to be given systemic steroids (44% versus 66%). They were equally likely to be admitted (24% versus 21%), but were less likely to be prescribed steroids if sent home (38% versus 64%). At the 2 week follow up interview the pregnant women were three times more likely to report an ongoing exacerbation of their asthma.<sup>37</sup>

Provided abdominal shielding is used, chest radiography results in minimal exposure of the fetus to ionising radiation and, if clinically indicated, this investigation must never be withheld just because the patient is pregnant.

#### Management during labour and delivery

Acute attacks of asthma during labour and delivery are extremely rare and women should be reassured accordingly. Women may continue their regular inhalers throughout labour. Those on oral steroids (>7.5 mg prednisolone daily for more than 2 weeks) at the onset of labour or delivery should receive parenteral steroids (hydrocortisone 100 mg 6–8 hourly) during labour, and until they are able to restart their oral medication.<sup>38</sup> Prostaglandin E<sub>2</sub> used to induce labour, to ripen the cervix, or for early termination of pregnancy is a bronchodilator and is safe. Prostaglandin F<sub>2 $\alpha$</sub> , indicated for severe postpartum haemorrhage, should be used with caution as it may cause bronchospasm.<sup>23</sup>

Asthmatic women may safely use all forms of pain relief in labour, including epidural analgesia and Entonox. In the unlikely event of an acute asthmatic attack, opiates should be avoided. If anaesthesia is required, women should be encouraged to have epidural rather than general anaesthesia because of the increased risk of chest infection and associated atelectasis. Ergometrine has been reported to cause bronchospasm, particularly in association with general anaesthesia, but this does not seem to be a practical problem when syntometrine (oxytocin/ergometrine) is used to prevent postpartum haemorrhage. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain relief following a caesarean section. Women with asthma should be asked about any known sensitivity to aspirin or NSAIDs before using these drugs.

#### Breast feeding

Women with asthma should be encouraged to breast feed. 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. This risk may be reduced by breast feeding. All inhaled preparations, oral steroids, and methylxanthines are safe when breast feeding.

#### Conclusion

Management of asthma in pregnancy does not differ significantly from management outside pregnancy. The priority should be effective control of the disease process, with the aim being total freedom from symptoms both day and night. The medications used to treat asthma are safe in pregnancy, but concerns on the part of pregnant women and their carers may result in the reduction, cessation, or withholding of important treatments. Great attention must therefore be given to explanation and reassurance about the safety, in pregnancy and during lactation, of the drugs used to treat asthma. Asthma care and obstetric care should be carefully integrated.<sup>22</sup> The small risk of harm to the fetus comes from poorly controlled severe disease rather than from the drugs used to prevent or treat asthma.

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