7 Asthma in pregnancy

7.1 NATURAL HISTORY AND MANAGEMENT OF STABLE ASTHMA

Several physiological changes occur during pregnancy that could worsen or improve asthma, but it is not clear which, if any, are important in determining the course of asthma during pregnancy. Pregnancy can affect the course of asthma and asthma and its treatment can affect pregnancy outcomes.

The natural history of asthma during pregnancy is extremely variable (and studies investigating this have been heterogeneous because of different severities of asthma included). In a prospective cohort study of 366 pregnancies in 330 asthmatic women, asthma worsened during pregnancy in 35%.[316] A more recent prospective cohort study of 1739 pregnancies showed an overall improvement in 23% and deterioration in 30.3%.[1] A systematic review showed no effect of pregnancy or stage of pregnancy on FEV_1 or FVC , although one study showed bronchial hyperresponsiveness to metacholine challenge improved in pregnancy in 69% of women (the greatest improvement being in the second trimester) but worsened in 31%.[2] The same authors showed that carrying a female fetus was associated with worse maternal asthma judged by diurnal variation of PEFR.[3] Studies suggest that 11-18% of pregnant women with asthma will have at least one emergency department visit for acute asthma and of these 62% will require hospitalisation.[317, 318] There is also some evidence that the course of asthma is similar in successive pregnancies.[316, 4] Severe asthma is more likely to worsen during pregnancy than mild asthma,[316] but some patients with very severe asthma may experience improvement, whilst symptoms may deteriorate in some patients with mild asthma. In a large US study, the rates of asthma exacerbation were 12.6%, 25.7% and 51.9% in those with mild, moderate and severe asthma respectively. The corresponding rates of hospitalisation were 2.3%, 6.8% and 26.9%.[1]

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B **Women with asthma should be counselled regarding the importance and safety of continuing their asthma medications during pregnancy to ensure good asthma control.**

B/C - Women should be advised that poorly controlled asthma may lead to adverse pregnancy outcomes (or 'is associated with increased problems for both mother and baby')

The conclusions of a meta-analysis of 14 studies is in agreement with the commonly quoted generalisation that during pregnancy about one third of asthma patients experience an improvement in their asthma, one third experience a worsening of symptoms, and one third remain the same.[319] A review of all studies examining the effect of pregnancy on the course of asthma concluded that the prospective studies agreed that an equal number of women improve, worsen or are unchanged.[5]

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In a large cohort study, the most severe symptoms were experienced by patients between the 24th and 36th week of pregnancy. Thereafter symptoms decreased significantly in the last four weeks and 90% had no asthma symptoms during labour or delivery. Of those who did, only two patients required anything more than inhaled bronchodilators.[316] A further study has confirmed the observation that the last month of pregnancy is the one in which patients are least likely to have an asthma exacerbation.[320] A systematic review concluded that the worsening of symptoms is most likely in the second and third trimesters, with the peak in the sixth month.[5]

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A cohort study comparing 198 pregnant women with asthma to 198 women without asthma reported that non-atopic patients with asthma tend to have more severe asthma. Pre-eclampsia was also more common in this group. However with adequate surveillance and treatment, pregnancy and delivery complications can be avoided.[321] A systematic review has shown that baseline asthma severity does determine what happens to the course of asthma in

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pregnancy and asthma may affect the risk of adverse outcomes.[322]

C **Monitor pregnant women with moderate/severe asthma closely because poorly controlled asthma is associated with poorer pregnancy outcomes.**

Uncontrolled asthma is associated with many maternal and fetal complications, including hyperemesis, hypertension, pre-eclampsia, vaginal haemorrhage, complicated labour, fetal growth restriction, preterm birth, increased perinatal mortality, and neonatal hypoxia.[323-326, 1] A large Swedish population-based study using record linkage data demonstrated increased risks for preterm birth, low birth weight, perinatal mortality and pre-eclampsia in women with asthma. The risks for preterm delivery and low birth weight were higher in women with more severe asthma necessitating admission.[327] 2+

A large prospective cohort study comparing moderate and severe asthma with controls found the only significant difference was an increased Caesarean section rate (OR 1.4, CI 1.1-1.8).[1] Logistic regression analysis of the severe group showed an increased risk of GDM (AOR 3(1.2-7.8)) and preterm delivery < 37 weeks (AOR 2.2(1.2-4.2)) but this could have been an effect of corticosteroids. In the Yale asthma study no effect of asthma symptoms or severity was seen on preterm delivery but oral steroids increased the rate and reduced gestation by 2.2 weeks AOR 1.05 (1.01-1.09).[6] Daily asthma symptoms were associated with an increased risk of fetal growth restriction (AOR 2.25 (1.25-4.06) and there was a 24% increase with each increased symptom step. This is supported by a systematic review of 4 studies that concluded asthma exacerbation in pregnancy increases the risk of low birth weight.[7] The RR was 2.54 (CI 1.52-4.25) compared to women without asthma. This review found no increase in preterm delivery or pre-eclampsia in those with acute exacerbations. In a large observational cohort study of 2123 women with asthma, there was an association of both mean FEV_1 and mean FEV_1 < 80% predicted with gestational hypertension, preterm delivery < 37 weeks, < 32 weeks and low birth weight.[8] The AOR for women with a mean FEV_1 < 80% predicted of a preterm birth < 37 weeks was 1.36 (1.01-1.84) and for a preterm birth < 32 weeks was 1.85 (1.05-3.28). In contrast, if asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.[317 318] Pregnancy should therefore be an indication to optimise therapy and maximise lung function in order to reduce the risk of acute exacerbation. 2++ 2+ 2++

☑ Advise women who smoke about the dangers for themselves and their babies and give appropriate support to stop smoking.

7.2 MANAGEMENT OF ACUTE ASTHMA IN PREGNANCY

The management of acute asthma in pregnancy may be affected by concerns about harmful effects of medication on the fetus. In a prospective controlled study of 51 pregnant women and 500 non-pregnant women presenting with acute asthma to an emergency department in Boston, USA, pregnant patients with asthma were less likely to receive appropriate treatment with steroids and, as a result, were more likely to experience ongoing exacerbation at two weeks.[328] Available studies give little cause for concern regarding treatment side effects (see section 7.3) and the maternal and fetal risks of uncontrolled asthma are much greater than the risks from using conventional asthma medications for management of acute asthma. In the last four confidential enquiries into maternal deaths in the UK (covering 1994-2005) there were seventeen deaths from asthma.[329 330 + 529a and b] 2+

Oxygen should be delivered to maintain saturation 94-98% in order to prevent maternal and fetal hypoxia.[9] When interpreting arterial blood gases in pregnancy it should be remembered that the progesterone-driven increase in minute ventilation may lead to relative hypocapnia and a respiratory alkalosis, and higher PaO2[10, 11] but oxygen saturations are unaltered.[12] Importantly, acidosis is poorly tolerated by the fetus. Drug therapy should be given as for a non-pregnant patient with acute asthma, including repeated doses of / ? continuous nebulised β_2 agonists and early administration of steroid tablets.[316 318 320 323 324] In severe cases, intravenous β_2 agonists, aminophylline, or intravenous bolus magnesium sulfate can be used 4

as indicated.[13] Continuous fetal monitoring should be performed when asthma is uncontrolled or severe, or when fetal assessment on admission is not reassuring. Consideration should be given to early referral to critical care services since due to impaired ventilatory mechanics in late pregnancy, the resulting lower functional residual capacity may result in earlier oxygen desaturation and planning may be required as pregnant women may be more difficult to intubate due to anatomical changes especially if they have pre-eclampsia.[14]

C **Give drug therapy for acute asthma as for the non-pregnant patient including systemic steroids and magnesium sulphate.**

D **Deliver high flow oxygen immediately to maintain saturation 94-98%.**

D **Acute severe asthma in pregnancy is an emergency and should be treated vigorously in hospital.**

☑ Continuous fetal monitoring is recommended for severe acute asthma.

☑ For women with poorly controlled asthma during pregnancy there should be close liaison between the respiratory physician and obstetrician, with early referral to critical care physicians for women with acute severe asthma.

7.3 DRUG THERAPY IN PREGNANCY

In general, the medicines used to treat asthma are safe in pregnancy.[331, 15] A large UK population based case-control study found no increased risk of major congenital malformations in children of women receiving asthma treatment in the year before or during pregnancy.[16] The risk of harm to the fetus from severe or chronically under-treated asthma outweighs any small risk from the medications used to control asthma. 2+

7.3.1 β_2 AGONISTS

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to short-acting β_2 agonists.[331, 332,15-17] A prospective study of 259 pregnant patients with asthma who were using bronchodilators compared with 101 pregnant patients with asthma who were not, and 295 control subjects, found no differences in perinatal mortality, congenital abnormalities, prematurity, mean birth weight, apgar scores or labour/delivery complications.[333] A case control study including 2460 infants exposed to short acting β_2 agonists found no increased risk of congenital malformations in exposed infants.[1] With regard to long-acting β_2 agonists (LABAs), evidence from prescription event monitoring suggests that salmeterol is safe in pregnancy[334] and although there are some data on formoterol, numbers are small.[18] Systematic review of studies including 190 exposures to LABA demonstrated no increased risk of congenital malformations, preterm delivery or pre-eclampsia.[19] The case control study by Tata et al included 156 infants exposed to LABA and no increased risk of major congenital malformations.[16] As in other settings, LABAs should be used with an inhaled corticosteroid, ideally as a combination product.[20] Data on the use of combination products in pregnancy are scarce although there are no theoretical reasons why these would be harmful. There are some safety data for seretide (salmeterol/fluticasone) but with small numbers.[21] 2+ 3

B **Use short acting β_2 agonists as normal during pregnancy.**

C **Use long acting β_2 agonists (LABA) as normal during pregnancy.**

7.3.2 INHALED STEROIDS

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to inhaled steroids.[331 335-338, 16, 19, 22] Inhaled anti-inflammatory treatment has been shown to decrease the risk of an acute attack of asthma in pregnancy[320] and the risk of readmission following asthma exacerbation.[318] A randomised placebo controlled trial of inhaled beclomethasone versus oral theophylline in moderate asthma in pregnancy showed no difference in the primary outcome of one or more asthma exacerbations resulting in medical intervention, but inhaled beclomethasone was better tolerated - the relative risk of withdrawal because of side effects was 0.3 (CI 0.1-0.9) for beclomethasone.[1] A meta-analysis of four studies of inhaled corticosteroid use in pregnancy showed no increase in the rate of major malformations, preterm delivery, low birth weight or pregnancy induced hypertension.[23] The UK case control study included 1429 infants exposed to inhaled steroids and found no increased risk of major congenital malformations.[16]

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B **Use inhaled steroids as normal during pregnancy.**

7.3.3 THEOPHYLLINES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to methylxanthines.[331 339]

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Theophylline was as effective as inhaled beclomethasone at preventing exacerbations in pregnant women with moderate asthma but 8.9 % of women withdrew from theophyline 300mg bd because of side effects.[1] For women requiring therapeutic levels of theophylline to maintain asthma control, measurement of theophylline levels is recommended. Since protein binding decreases in pregnancy, resulting in increased free drug levels, a lower therapeutic range is probably appropriate.[340]

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C **Use oral and intravenous theophyllines as normal during pregnancy.**

D **Check blood levels of theophylline in acute severe asthma and in those critically dependent on therapeutic theophylline levels.**

7.3.4 STEROID TABLETS

Exposure to oral corticosteroids in the first trimester *may* slightly increase rates of cleft lip and palate [24] however this has not been substantiated in all studies [25, 26, 341, 16, 27]

A body of evidence suggests that steroid tablets are not teratogenic.[323 331 341] Data from many studies have failed to demonstrate an association between first trimester exposure to steroid tablets and oral clefts.[341, 27] Although one meta-analysis found an increased risk,[342] a prospective study by the same group found no difference in the rate of major birth defects in prednisolone-exposed and control babies.[342] One case control study that may have influenced the findings of the meta-analysis found a significant association between exposure to steroids in the first trimester and an increased risk of cleft lip,[343] although this increase is not significant if only paired controls are considered. A more recent population based case control study revealed a crude odds ratio of corticosteroid exposure from four weeks before through 12 weeks after conception of 1.7 (95% CI, 1.1-2.6) for cleft lip.[24] However another case control study[16] including 262 exposed infants found no such association, although this was not limited to first trimester exposure.

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Even if the association is real, the benefit to the mother and the fetus of steroids for treating a life-threatening disease justify their use in pregnancy.[323, 10] Pregnant women with acute asthma exacerbation are less likely to be treated with steroid tablets than non-pregnant women.[328] This failure to administer steroid tablets when indicated increases the risk of ongoing exacerbation and therefore the risks to the mother and her fetus.

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Some studies have found an association between steroid tablet use and pregnancy-induced hypertension or pre-eclampsia, preterm labour[321] and fetal growth but severe asthma may be a confounding variable.[28] 2+

C **Use steroid tablets as normal when indicated during pregnancy for severe asthma. Steroid tablets should never be withheld because of pregnancy. (First trimester exposure to oral steroids may slightly increase the risk of oral cleft lip / palate). Women should be advised that the benefits of treatment with oral steroids outweigh the risks.**

7.3.5 LEUKOTRIENE RECEPTOR ANTAGONISTS

Data regarding the safety of leukotriene antagonists in pregnancy are limited. Animal studies and post-marketing surveillance for zafirlukast with 28 pregnancies with 20 exposed in the first trimester and montelukast are reassuring.[29] There are animal data of concern for zileuton.[344] A case control study with 96 cases exposed to LTRAs found no increased risk of major malformations between women with asthma exposed to LTRA and women with asthma taking only beta agonists.[28] A systematic review found no increased risk of malformations or preterm delivery in nine exposed women.[6, 19] 2-4 2+ 2++

D **Leukotriene antagonists (LTRA) may be continued in women who have demonstrated significant improvement in asthma control with these agents prior to pregnancy not achievable with other medications.**

7.3.6 CHROMONES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to chromones.[330 33119, 28] 2+

C **Use chromones as normal during pregnancy.**

7.3.7 IMMUNOMODULATION THERAPY

There are as yet no clinical data on the use of omalizumab for moderate-severe allergic asthma in pregnancy. There are some reassuring animal studies re teratogenicity (classed as FDA category B). A registry of pregnancy exposures ('EXPECT') is currently being taken by Novartis pharmaceuticals.

7.4 MANAGEMENT DURING LABOUR

Acute attacks of asthma are very rare in labour due to endogenous steroid production. In women receiving steroid tablets there is a theoretical risk of maternal hypothalamic-pituitary-adrenal axis suppression. Women with asthma may safely use all forms of pain relief in labour.

In some studies there is an association between asthma and an increased caesarean section rate,[321 345 346] but this may be due to planned caesarean sections[320] or inductions of labour rather than due to any direct effect of asthma on intrapartum indications. A large prospective cohort study comparing moderate and severe asthma with controls found the only significant difference was an increased Caesarean section rate (OR 1.4, CI 1.1-1.8).[1] 2+

Data suggest that the risk of postpartum exacerbation of asthma is increased in women having caesarean sections.[345] This may relate to the severity of their asthma rather than to the caesarean section, or to factors such as postoperative pain with diaphragmatic splinting, hypoventilation and atelectasis. Prostaglandin E2 may safely be used for labour inductions.[340] Prostaglandin F2α (carboprost/hemobate®) used to treat postpartum haemorrhage due to uterine atony may cause bronchospasm.[340] Although ergometrine may cause bronchospasm particularly in association with general anaesthesia,[340] this is not a problem encountered when syntometrine (syntocinon/ergometrine) is used for postpartum haemorrhage prophylaxis. 2- 3

Although suppression of the fetal hypothalamic-pituitary-adrenal axis is a theoretical possibility with maternal systemic steroid therapy, there is no evidence from clinical practice or the literature to support this.[347]

☑ Advise women that acute asthma is rare in labour.

☑ Advise women to continue their usual asthma medications in labour.

☑ In the absence of acute severe asthma, reserve caesarean section for the usual obstetric indications.

C **If anaesthesia is required, regional blockade is preferable to general anaesthesia in women with asthma.**

☑ Women receiving steroid tablets at a dose exceeding prednisolone 7.5 mg per day for more than two weeks prior to delivery should receive parenteral hydrocortisone 100 mg 6-8 hourly during labour.

D **Use prostaglandin F2α with extreme caution in women with asthma because of the risk of inducing bronchoconstriction.**

7.5 DRUG THERAPY IN BREASTFEEDING MOTHERS

The medicines used to treat asthma, including steroid tablets, have been shown in early studies to be safe to use in nursing mothers.[350] There is less experience with newer agents. Less than 1% of the maternal dose of theophylline is excreted into breast milk.[350] 2+

Prednisolone is secreted in breast milk, but milk concentrations of prednisolone are only 5-25% of those in serum.[351] The proportion of an oral or intravenous dose of prednisolone recovered in breast milk is less than 0.1%.[351-353] For maternal doses of at least 20 mg once or twice daily the nursing infant is exposed to minimal amounts of steroid with no clinically significant risk.[351-353] 2+ 3

C **Encourage women with asthma to breastfeed.**

C **Use asthma medications as normal during lactation, in line with manufacturer's recommendations.**

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