

# Asthma in Pregnancy

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## KEYWORDS

- Asthma • Pregnancy • Exacerbation
- Inhaled corticosteroid

## ASTHMA DURING PREGNANCY

### *What is the Prevalence of Asthma During Pregnancy?*

The burden of asthma in pregnancy is increasing worldwide,<sup>1,2</sup> with European estimates of at least 4% of women having asthma,<sup>3</sup> and at least 8% of women in antenatal clinics in the United Kingdom having asthma.<sup>4</sup> Increases in asthma prevalence have also been reported in the United States<sup>1</sup> from around 3% to more than 8% since 1994.<sup>2</sup> In Australia the prevalence of asthma in pregnancy is 12%.<sup>5</sup> As the most common respiratory disorder to complicate pregnancy, asthma represents a significant public health issue. Adequate asthma treatment and careful management is the key to a successful pregnancy outcome for these mothers and babies.

### *Can Changes in Asthma Be Expected in Pregnancy?*

Most women with asthma experience a change in their disease control while pregnant. While for one-third this is an improvement, for at least one-third of women it is a worsening.<sup>6,7</sup> These changes are unpredictable from woman to woman and from pregnancy to pregnancy,<sup>8</sup> necessitating careful regular review of asthma during pregnancy. In the 1980s, subjective questionnaires completed by a large prospective cohort of 330 pregnant

women in the United States provided evidence of the “one-third hypothesis,” indicating that among women who rated their asthma as having worsened, symptoms of wheeze and sleep and activity limitation due to asthma were significantly increased between 25 and 32 weeks’ gestation.<sup>7</sup> Among women reporting an improvement, however, there was a decrease in wheeze and little change in sleep/activity interference. These observations suggested that asthma control (wheezing, nocturnal asthma, activity limitation) is altered in the latter stages of pregnancy.

Until recently, few studies had assessed asthma changes during pregnancy using objective measures.<sup>9–11</sup> Studies in the 1970s and 1980s among small cohorts of women found no pregnancy-related changes in lung function measured by spirometry in either asthmatic or non-asthmatic women.<sup>9,11</sup> Juniper and colleagues<sup>9,12</sup> described an overall improvement in methacholine airway responsiveness in the second trimester compared with preconception; however, no relationship with serum progesterone or estradiol concentrations was found. Peak expiratory flow values have recently been analyzed throughout pregnancy and have been found to increase with each trimester in a cohort of 43 women with asthma.<sup>13</sup> It is possible that the increase in progesterone with advancing gestation contributes to cyclic adenosine monophosphate (cAMP)-induced

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bronchodilation, thereby improving asthma and peak flow.<sup>13</sup> Also recently analyzed were changes in asthma severity from a cohort of 641 pregnant women with asthma, for whom medication use and asthma symptoms had been recorded several times through the second half of pregnancy.<sup>14</sup> Severity before pregnancy and in each month of pregnancy was described as intermittent, mild persistent, or moderate/severe, according to the Global Initiative for Asthma (GINA) guidelines. There was little evidence of any pregnancy-specific changes in asthma severity when data were stratified by prepregnancy severity rating; however, the measure of severity as a GINA category lacks sensitivity. The only group that had a significant change was the mild persistent group, where severity was reduced in months 6 and 9 compared with the second month. Among the factors analyzed (race, age, atopic status, prepregnancy asthma severity, body mass index [BMI], parity, fetal sex, smoking, and use of medication according to guidelines), only the prepregnancy severity and medication use was related to changes in asthma severity during pregnancy, with prepregnancy status predicting worse asthma in pregnancy, and lack of appropriate medication use being related to more severe asthma in pregnancy.<sup>14</sup>

A potentially useful objective marker of airway inflammation in asthma is fractional exhaled nitric oxide (FENO). In a small cross-sectional study, Tamasi and colleagues<sup>15</sup> found that FENO was not altered by pregnancy itself, but among pregnant women with asthma FENO was correlated with the level of asthma control. Unfortunately measures of FENO were not taken prospectively through pregnancy, so any effect of the stage of pregnancy on this inflammatory marker is unknown. Further studies are required to elucidate the predictors for clinically relevant changes in asthma control during pregnancy.

### ***What are the Risk Factors for Asthma Exacerbations During Pregnancy?***

Exacerbations are an important clinical feature of asthma and when severe, may require hospitalization. During pregnancy, around 5.8% of women are hospitalized with an exacerbation of asthma,<sup>16</sup> with some studies reporting more than 20% of women having exacerbations requiring medical intervention, including hospitalization, unscheduled doctor visits, and use of emergency therapy.<sup>17,18</sup> Even among well-managed cohorts, the exacerbation rate is high.<sup>18,19</sup> In Australia, 36% of women had a severe exacerbation requiring medical intervention for asthma during

pregnancy and a further 19% had a mild exacerbation during pregnancy.<sup>19</sup>

While exacerbations may occur at any time during gestation, they appear to be more common in the late second trimester.<sup>6,19–21</sup> A Canadian study found that visits to the emergency department for asthma exacerbations was clearly distinct from visits for other reasons, peaking in the second trimester and falling as gestation advanced.<sup>22</sup> Asthma exacerbations are unlikely to occur during labor and delivery<sup>7,23–25</sup>; however, one study described 46% of women with severe asthma having symptoms during labor.<sup>18</sup>

Women with severe asthma are most likely to experience exacerbations in pregnancy.<sup>6,18,19,26</sup> In one study, severe exacerbations requiring medical intervention occurred among 8% of women with mild asthma, 47% of women with moderate asthma, and 65% of women with severe asthma.<sup>19</sup> Women with severe exacerbations in pregnancy have significantly lower asthma-specific quality of life, which may be a more sensitive measure of limitations due to asthma than symptoms alone.<sup>27</sup> The effects of atopy, sinusitis, and gastroesophageal reflux on exacerbations require further investigation, as these conditions may worsen in pregnancy leading to an exacerbation of asthma.<sup>28</sup> Other risk factors for exacerbation during pregnancy include inadequate prenatal care,<sup>29,30</sup> obesity,<sup>14,31</sup> and lack of appropriate treatment with inhaled corticosteroids.<sup>19–21,32</sup> Almost one-third of women self-reported nonadherence to prescribed inhaled corticosteroid (ICS) medication before a severe exacerbation.<sup>19</sup> In Finland, the risk of having an exacerbation was reduced by more than 75% among women who were regular users of ICS.<sup>21</sup> More recent data demonstrated a higher rate of emergency department and physician visits during pregnancy among women who did not use ICS before pregnancy.<sup>32</sup> Improvements in asthma management that address the issue of ICS nonadherence may reduce the exacerbation rate among pregnant women.

There are limited data addressing the causal factors of severe asthma exacerbations during pregnancy; however, several studies have suggested that respiratory tract viral infections may be common contributors,<sup>19,20,33,34</sup> as they are in children and nonpregnant adults.<sup>35</sup> Viral infection was the most common self-reported cause of severe asthma exacerbations, reported by 34% of women.<sup>19</sup> Pregnant women may be more susceptible to viral infection, due to changes in cell-mediated immunity during pregnancy.<sup>6</sup> Pregnant women and those with asthma are certainly 2 groups with significantly increased susceptibility to infection with influenza strains, including

seasonal and H1N1 influenza.<sup>36,37</sup> In the early stages of the H1N1 pandemic in the United States, 7% of hospitalized patients were pregnant, with 22% of these women also having asthma.<sup>36</sup> In total 9% of all admissions to intensive care units and 16% of all deaths were among pregnant women, indicating that both the prevalence of illness and its severity is increased with pregnancy.<sup>36</sup> Specific studies of cohorts of pregnant women have shown that those with asthma were more likely to have an upper respiratory tract or urinary tract infection during pregnancy than those without asthma, with severe asthma being associated with significantly more infections than mild asthma.<sup>38</sup> However, this evidence comes from a retrospective study relying on self-report of infection, and further evaluation using a prospective study design with objective confirmation of viral infection and specific identification of the viruses responsible may provide useful data. A study from New York suggested that prevention of infection may improve asthma symptoms among pregnant women, demonstrating an improvement in asthma symptoms during pregnancy among 50% of women who received an influenza vaccine, compared with improvement among only 15% of women not receiving the vaccine.<sup>39</sup>

### ***What are the Mechanisms for Changes in Asthma During Pregnancy?***

Over the years the involvement of hormones, altered immune function, and fetal sex in pregnancy-related changes in asthma have been proposed as mechanisms. Increases in maternal hormones during pregnancy may contribute to physiologic changes that result in improved asthma, for example, the promotion of anti-inflammatory effects by the increase in serum free cortisol.<sup>34,40</sup> Progesterone may contribute to improved asthma via increased minute ventilation,<sup>41</sup> smooth muscle relaxation,<sup>42</sup> or cAMP-induced bronchodilation.<sup>13</sup> On the other hand, progesterone may contribute to worsening asthma via changes in  $\beta_2$ -adrenoreceptor responsiveness and airway inflammation.<sup>43</sup> Among nonpregnant women, a high proportion of asthmatics have an abnormal concentration of either progesterone or estradiol compared with nonasthmatics,<sup>44</sup> which may explain why the progression of asthma during pregnancy differs between women.

A novel marker of the immunotolerance of pregnancy is heat shock protein (Hsp) 70, which is decreased in the circulation of healthy pregnant women as compared with nonpregnant adults.<sup>45,46</sup> Women with asthma have higher levels of Hsp70 than their nonasthmatic counterparts;

however, the role of this marker in chronic inflammation of asthma and its potential relationship with perinatal outcomes of these pregnancies requires further investigation.<sup>46</sup> Other alterations in the maternal immune system during pregnancy such as a suppression of cell-mediated immunity, and the development of a predominantly Th2 cytokine environment, which is essential for fetal survival,<sup>47</sup> may contribute to changes in asthma. Th2 cytokine polarization typical of allergic asthma may be heightened by the Th2 polarization of pregnancy. The placenta has a very high Th2:Th1 cytokine ratio, which was further elevated in samples collected from women with asthma who did not use ICS treatment during pregnancy.<sup>48</sup> In a cross-sectional analysis, interleukin (IL)-4 and interferon- $\gamma$ -producing T-lymphocyte subsets were found to be significantly increased in pregnant women with asthma, compared with healthy pregnant women and nonpregnant asthmatic women.<sup>49</sup> However, this was not related to whether women perceived their asthma to have improved or worsened during pregnancy.<sup>49</sup> In a recent study, there was no evidence of enhanced lymphocyte activation among pregnant women with asthma as compared with healthy pregnant women.<sup>50</sup> In addition, no differences in maternal IL-6, IL-8, eotaxin, and RANTES concentrations were found in the peripheral blood of pregnant women with asthma in the third trimester, compared with pregnant controls.<sup>51</sup> However, bronchial epithelial cells demonstrated increased production of IL-8 and sICAM-1 in the presence of plasma from pregnant women with asthma, and results were suggestive of an increased chemotactic capacity,<sup>52</sup> which may be a mechanism contributing to worsening asthma in some pregnant women.

It has been hypothesized that the progression of maternal asthma symptoms in pregnancy may be influenced by the sex of the fetus.<sup>53–56</sup> Recently, Bakhireva and colleagues<sup>57</sup> demonstrated that women pregnant with a female fetus had a higher incidence of hospitalization for asthma during pregnancy. However, other reports do not support this association.<sup>8,22,58</sup> The largest study in this area of more than 10,000 asthmatic pregnancies in Quebec found no differences between women pregnant with male and female fetuses with regard to the occurrence of severe exacerbations, or the use of ICS or short-acting  $\beta_2$ -agonist (SABA) treatment.<sup>58</sup>

### **CHANGES IN ASTHMA AFFECT BOTH MOTHER AND BABY**

In addition to the effect of pregnancy on asthma, it has been well described that asthma affects

a wide range of pregnancy outcomes, related to both the mother (Table 1) and the neonate (Table 2). However, there is conflicting evidence in the literature regarding these effects, possibly due to sizeable variation in study design, sample size, and confounding factors in each published report. Many of the studies reporting increased risk of perinatal complications with asthma have been large database studies, whereas many of the studies not finding increased risks have been among smaller, yet better managed cohorts of pregnant women. It is possible and likely that better management of asthma improves outcomes among pregnant women; however, smaller clinical studies may also lack the power to detect increased risks in this population.

### ***Is Asthma Associated with Poor Maternal Outcomes in Pregnancy?***

In several prospective and retrospective cohort studies, pregnant women with asthma have been identified as being at increased risk of pregnancy-induced hypertension (PIH) or preeclampsia.<sup>21,25,59–69</sup> For example, in Finland, 15% of women with asthma developed preeclampsia compared with 5% of women without asthma, with the rate even higher at 25% among women using oral steroids.<sup>25</sup> A relationship between oral steroid use, but not ICS use, and the development of PIH was also described by a case-control study.<sup>70</sup> Another study found that women with moderate to severe symptoms during pregnancy were at increased risk of preeclampsia, suggestive of a role of active maternal inflammation,<sup>68</sup> while others have described an association with reduced lung function.<sup>71</sup>

However, there are also numerous reports from prospective<sup>23,38,72–74</sup> and retrospective cohort studies<sup>75,76</sup> that do not find an increased risk of

preeclampsia or PIH among pregnant women with asthma. In particular, a study of 486 pregnant women with actively managed asthma and 486 matched controls demonstrated no increased risk on this and other perinatal complications,<sup>73</sup> suggesting that asthma that is well controlled does not have significant adverse effects on either the mother or baby.

There is no evidence that asthma exacerbations in pregnancy are associated with an increased risk of preeclampsia.<sup>16,21,70,73,74</sup> In other studies, exacerbations prior to pregnancy increased the risk of PIH and pre-eclampsia,<sup>70,77</sup> suggesting that the underlying severity of asthma is an important factor.

Together, these studies suggest that severity, rather than control or exacerbations, may be related to the increased risk of preeclampsia in asthmatic women, possibly due to a common pathogenesis of the 2 diseases, such as mast cell infiltration into the smooth muscle of both the lungs and myometrium.<sup>78</sup> Preeclampsia has been associated with airway hyperresponsiveness.<sup>78</sup> Measurements in postpartum women with and without asthma indicated that those with a history of preeclampsia required significantly less methacholine to produce a 20% decrease in lung function, compared with women with previously normotensive pregnancies. Vascular hyperreactivity is another potential mechanism leading to changes in uteroplacental blood flow observed in vitro in placentas from women with moderate and severe asthma<sup>79</sup> and women with preeclampsia.<sup>80</sup>

Few studies have been specifically designed to test an association between maternal asthma and gestational diabetes. However, many large studies have examined this outcome, along with others, and have concluded that there is no increased risk in women with asthma.<sup>21,23,25,38,59,66,72–74</sup> Some studies<sup>62,65,69,76</sup> did find an increased risk

**Table 1**  
Cohort studies examining the risk of maternal complications of pregnancy with asthma

Maternal Outcome	Number of Studies		Association of Outcome with Asthma Exacerbations in Pregnancy
	Increased Risk with Maternal Asthma <sup>a</sup>	No Effect of Maternal Asthma <sup>a</sup>	
Preeclampsia or pregnancy-induced hypertension	13 <sup>21,25,59–69</sup>	7 <sup>23,38,72–76</sup>	No
C section	13 <sup>4,25,61,62,64,65,69,72,74,76,81–83</sup>	3 <sup>23,66,75</sup>	No
Gestational diabetes	4 <sup>62,65,69,76</sup>	9 <sup>21,23,25,38,59,66,72–74</sup>	No

<sup>a</sup> Compared with women without asthma.

**Table 2**  
**Cohort studies examining the risk of fetal and neonatal complications with maternal asthma**

Fetal/Neonatal Outcome	Number of Cohort Studies		Association of Outcome with Asthma Exacerbations in Pregnancy
	Increased Risk with Maternal Asthma <sup>a</sup>	No Effect of Maternal Asthma <sup>a</sup>	
Congenital malformations	3 <sup>61,109,110</sup>	8 <sup>4,17,21,23,64,72,73,76</sup>	Yes
Perinatal mortality	3 <sup>60,88,108</sup>	9 <sup>5,21,23,25,69,72–74,82</sup>	No
Preterm labor or delivery	11 <sup>59,60,61,64,65,69,72,76,86,87,98</sup>	7 <sup>5,17,21,23,38,73,75</sup>	Yes
Low birth weight or intrauterine growth restriction	13 <sup>4,5,23,56,59,60,61,64,76,81,83,85,86</sup>	8 <sup>26,38,66,72,73,82,87,88</sup>	Yes
Neonatal sepsis	1 <sup>72</sup>	1 <sup>4</sup>	No
Transient tachypnea of the newborn	3 <sup>4,61,121</sup>	1 <sup>72</sup>	No

<sup>a</sup> Compared with women without asthma.

of gestational diabetes, and in one of these the increased risk occurred in oral steroid–dependent asthmatics only.<sup>76</sup>

### ***Is Asthma Associated with Increased Medical Intervention During Labor and Delivery?***

Many studies of both prospective and retrospective design have concluded that maternal asthma is a risk factor for delivery by cesarean (C) section.<sup>4,25,61,62,64,65,69,72,74,76,81–83</sup> However, the majority of these studies have described either total C sections or elective C sections only, with one study specifically showing an increase in C sections for fetal distress.<sup>76</sup> Although there was an increase in total C sections among mothers with asthma, Dombrowski and colleagues<sup>72</sup> found no increase in C sections for fetal distress compared with mothers without asthma. Similarly, Clark and colleagues<sup>4</sup> showed an increase in elective C sections among women with asthma, but no increase in emergency C sections. In the large Swedish Medical Birth Registry study, the increased risk remained after excluding women with medical conditions associated with C delivery, such as preeclampsia, premature rupture of membranes, and gestational diabetes.<sup>62</sup> Some studies have found an increase in complications such as placental abruption<sup>62,84</sup> and premature rupture of membranes,<sup>69,76</sup> which may contribute to the higher rate of C sections among women with asthma.

### ***Is Asthma Associated with Poor Neonatal Outcomes?***

The literature has been somewhat divided on the effect of maternal asthma on fetal growth. The majority of cohort studies that report an increased risk of intrauterine growth restriction or low birth weight (<2500 g) among women with asthma have been retrospective in design,<sup>4,5,59,60,61,64,76,81,83,85</sup> with fewer prospective cohorts demonstrating this risk.<sup>23,56,86</sup> However, the majority of studies reporting no increased risk are prospective in design,<sup>26,38,66,72,73,87</sup> with fewer retrospective cohorts finding no risk.<sup>82,88</sup> These findings may indicate a lack of power to detect a risk of fetal growth restriction among smaller prospective studies, or may be related to the level of asthma control among the subjects in these studies, which may be improved by participation in a prospective study.

Two explanations for an increased risk of low birth weight are supported by the current literature. The first is that ICS use protects against this perinatal outcome, and the second is that maternal exacerbations are a risk factor for low birth weight. Data from 4 studies in which women did not use ICS treatment for asthma during pregnancy<sup>60,75,81,88</sup> was combined in a meta-analysis.<sup>89</sup> There was a significantly increased risk of low birth weight in these asthmatic pregnancies compared with pregnancies without asthma (relative risk [RR] 1.55, 95% confidence interval [CI] 1.28, 1.87). Conversely, the meta-analysis of data from 5 studies in which some or all women

had used ICS during pregnancy<sup>23,66,73,81,86</sup> demonstrated no significantly increased risk of low birth weight in women with asthma compared with those without asthma (RR 1.19, 95% CI 0.97, 1.45). Olesen and colleagues<sup>85</sup> assessed ICS use using a prescriptions database, and found that birth weights were lower among women who reduced their ICS use during pregnancy as compared with women who increased ICS use during pregnancy.

Data from 3 studies that described exacerbations during pregnancy as recurrent attacks of severe asthma or status asthmaticus,<sup>88</sup> hospitalization for asthma,<sup>23</sup> or acute asthma managed in the emergency department or clinic with nebulized bronchodilators<sup>73</sup> were combined in a meta-analysis.<sup>16</sup> Women who had an asthma exacerbation during pregnancy were at significantly increased risk of having a low birth weight neonate compared with women without asthma (RR 2.54, 95% CI 1.52, 4.25), whereas women without exacerbations were not at increased risk of low birth weight when compared with women without asthma (RR 1.12, 95% CI 0.8, 1.40). This analysis indicates that severe exacerbations increase the risk of low birth weight by more than 2.5-fold in women with asthma during pregnancy. This result is supported by studies that have described the reduction in mean birth weight among these women, finding that compared with women without exacerbations or a nonasthmatic group, severe exacerbations are associated with significant reductions in birth weight of between 56 and 434 g.<sup>17,23,67,90</sup> Recent work has also demonstrated an increased risk of small for gestational age babies among women with moderate or severe asthma, compared with women with mild asthma.<sup>91</sup>

Exacerbations of asthma during pregnancy are associated with an increased risk for low birth weight,<sup>16</sup> with a similar effect size to that of maternal smoking during pregnancy, which doubles the risk of low birth weight.<sup>92</sup> A direct effect of chronic maternal hypoxia on fetal growth via reduced fetal oxygenation, or indirect effects of alterations in placental vascular composition, blood flow, or function are possible mechanisms.<sup>48,56,79,93–97</sup>

Many cohort studies suggest an increased risk of preterm labor or delivery in pregnant women with asthma.<sup>59,60,61,64,65,69,72,76,86,87,98</sup> However, there are also several cohort studies showing no increased risk of preterm labor or delivery with maternal asthma.<sup>5,17,21,23,38,73,75</sup> Some of the larger prospective cohort studies have suggested that the effect of asthma on preterm birth may be related to the use of oral steroids during

pregnancy.<sup>72,86,99</sup> The increased odds of preterm delivery was 2.2<sup>72</sup> in one study and 1.1 in another.<sup>86</sup> The effects of severe asthma and/or severe asthma exacerbations are difficult to separate from the effects of the oral steroids themselves. A meta-analysis<sup>16</sup> of 4 studies<sup>21,23,73,88</sup> found that severe exacerbations were not a significant risk factor for preterm delivery. Despite this, a North American study that evaluated asthma control by interview prospectively during pregnancy and postpartum found a higher rate of preterm delivery among women with inadequate asthma control in early pregnancy compared with those with adequate control, and among women who were hospitalized for asthma during pregnancy compared with those not hospitalized.<sup>100</sup> These relationships remained significant after adjustment for confounders such as age, BMI, smoking, and socioeconomic status.<sup>100</sup> A relationship has also been described between lower lung function and premature birth, consistent with the concept that more severe asthma is a risk factor.<sup>71</sup> Reduced lung function may also be a marker of poor control of asthma, which influences preterm delivery via hypoxic mechanisms.<sup>71</sup> The release of inflammatory mediators from the mother as a result of asthma may also be involved,<sup>89</sup> given the association between other active inflammatory diseases such as rheumatoid arthritis and low birth weight or preterm delivery.<sup>101–103</sup>

The risk of preterm labor among women with asthma has been found to be increased among African Americans as compared with white Americans,<sup>104</sup> suggesting that socioeconomic status or ethnicity may be a confounder and risk factor for poor maternal outcomes during asthmatic pregnancies. Similar findings from other studies suggest that poor prenatal care or lack of education about asthma may contribute to adverse perinatal outcomes.<sup>30,69</sup> Another potential mechanism is that a common pathogenic pathway leads to hyperactivity of both the bronchial and myometrial smooth muscle, leading to preterm labor in women with asthma.<sup>87,105,106</sup> One study demonstrated that mothers of premature infants had evidence of airway hyperactivity,<sup>105</sup> but this was not confirmed by another group examining airway responsiveness in mothers of premature or low birth weight children.<sup>107</sup>

### ***Is Asthma Associated with Perinatal Mortality?***

Until recently, there were few studies adequately powered to determine the effect of asthma or asthma exacerbations on perinatal mortality.

Before the introduction of ICS treatment for asthma, a study by Gordon and colleagues<sup>88</sup> studied 277 women with actively treated asthma. Sixteen of these women had severe asthma characterized by regular acute attacks or status asthmaticus during pregnancy. Almost 40% of these women had either a spontaneous abortion, fetal death, or neonatal death.<sup>88</sup> Another study in the 1970s that extracted data on 381 women with asthma and more than 112,000 controls from the Norwegian medical birth registry found a significantly higher rate of neonatal mortality with maternal asthma, but no significant increase in still births, perinatal mortality, or infant mortality.<sup>60</sup> In more recent reports, cohort studies examining still birth and perinatal or neonatal mortality in women with asthma have found no increased risk as compared with women without asthma.<sup>5,21,23,25,69,72–74,82</sup> One exception to this was the much larger 2009 study by Canadian investigators Breton and colleagues.<sup>108</sup> Their study showed an increased odds of perinatal mortality (including still birth after 20 weeks' gestation, and neonatal death up to 29 days) among the 13,100 women with asthma compared with the 28,042 women without asthma (odds ratio [OR] 1.35, 95% CI 1.08, 1.67). However, this was no longer significant when adjusted for birth weight and gestational age, suggesting that the higher rates of low birth weight and premature delivery among women with asthma may be contributing to the increased risk of perinatal mortality.<sup>108</sup>

### ***Is Asthma Associated with Congenital Malformations?***

The majority of cohort studies on the risk of congenital malformations in women with asthma have shown no increased risk.<sup>4,17,21,23,64,72,73,76</sup> However, it is likely that many were underpowered to detect a difference in rare outcomes such as malformations, and over the last few decades treatments for asthma have changed. Larger and more recent studies suggest that there is an increased risk of congenital anomalies among women with asthma.<sup>61,109,110</sup> Extensive examination of data from administrative databases in Quebec has revealed that pregnant women with asthma have a 30% increased risk of any congenital malformation and a 34% increased risk of a major congenital malformation, compared with women without asthma.<sup>109</sup> The risk for women using antiasthmatic medications in the Swedish Medical Birth Register studies was smaller, at 9%.<sup>110</sup> A case-control study from the United Kingdom has also

identified a slight increased risk of any malformations among children of asthmatic mothers (OR 1.10, 95% CI 1.01, 1.20).<sup>111</sup>

It is unclear whether this increased risk is caused by the disease itself or the use of medications, but several clues are emerging. A prescriptions database was used to specifically estimate ICS dose in the first trimester in more than 4500 women with asthma, and a significantly reduced risk of malformations among users of moderate-dose ICS compared with nonusers was described.<sup>112</sup> Further research by this group in a larger cohort of 13,280 asthmatic pregnancies identified a 63% increased risk of malformations among users of high doses of ICS in the first trimester, compared with users of lower doses.<sup>113</sup> This work adds to evidence for the safety of lower doses of ICS, suggesting that doses be minimized to maintain asthma control in order to lessen potential risks of high doses of these medications. Among a cohort of 4344 asthmatic women, severe exacerbations in the first trimester were associated with an increased risk of any malformation as compared with women with no exacerbation of asthma.<sup>114</sup> These data were not supported by the United Kingdom case-control study, which found no relationship between clinically reported exacerbations and congenital malformations.<sup>111</sup>

Specific malformations for which maternal asthma has been found to be a risk factor include malformations of the nervous system (not including spina bifida), respiratory system and digestive system,<sup>109,115</sup> cardiac defects, and orofacial clefts.<sup>110</sup> A case-control study demonstrated that the risk of gastroschisis was increased among women using bronchodilators in the month before conception and during the first trimester, compared with nonusers of medication (adjusted OR 2.06, 95% CI 1.19, 3.59).<sup>115</sup> In a case-control study, pregnant women with asthma who used medication were also at twice the risk of heart defects.<sup>116</sup> Case-control studies have also provided evidence for an increased risk of oral clefts when women used oral steroids during the first trimester of pregnancy.<sup>117,118</sup> However, studies were not specifically conducted in asthmatic women, so the implications for them are unclear.

Studies that have examined the effects of specific asthma treatments on malformations have found no increased risk of malformations among users of budesonide.<sup>119,120</sup> One study described a significant but small increased risk of malformations in women using any drugs for asthma during pregnancy, compared with the rate of malformations in the whole population.<sup>110</sup>

### ***Is Asthma Associated with Neonatal Complications?***

There is relatively limited literature examining the relationship between maternal asthma and complications such as neonatal sepsis and transient tachypnea of the newborn. Neonatal sepsis was identified as an adverse outcome in women with mild asthma only<sup>72</sup> while another study did not find an association between asthma and neonatal sepsis, although women were not stratified by asthma severity.<sup>4</sup> In a retrospective cohort study in the United Kingdom, of more than 700 women with asthma and 700 controls without asthma, there was an increased rate of neonatal hospitalizations when mothers had asthma with an increased rate of transient tachypnea of the newborn.<sup>4</sup>

### ***Is Maternal Asthma Associated with Long-Term Changes into Childhood?***

Despite the increased risks of perinatal complications in women with asthma, there are few data available on longer-term health outcomes of children with asthmatic mothers. To date, increases in the prevalence of wheeze<sup>121</sup> and respiratory diseases,<sup>122</sup> left-handedness,<sup>123</sup> and mild to moderate intellectual disability<sup>124</sup> have been described. Schatz and colleagues<sup>125</sup> published the only follow-up of infants from a cohort of asthmatic women followed through pregnancy, and found that at 15 months of age, mental and psychomotor developmental outcomes were similar to those in children of nonasthmatic mothers.

Recent analysis has revealed that the children of asthmatic mothers are more at risk of asthma themselves when the mother's asthma is inadequately controlled during pregnancy.<sup>126</sup> In particular, during the first 10 years of life, children were at greater risk of asthma (adjusted OR 1.27, 95% CI 1.06, 1.52) when their mothers had asthma of moderate to severe severity that was also uncontrolled during pregnancy.<sup>126</sup> Asthma was considered uncontrolled when the mothers used high doses of SABA, or had severe exacerbations, including use of oral steroids, emergency department visits, or hospitalizations for asthma in the pregnancy.<sup>127</sup> In addition, children of asthmatic mothers had an 11% increased risk of atopic dermatitis, but this was not associated with maternal asthma severity or control during pregnancy.<sup>127</sup> Infants were more likely to have been prescribed antibiotics in the first 6 months of life when their mothers had asthma.<sup>127</sup> These data indicate that maternal asthma is a risk factor for childhood asthma, and that this risk could be

reduced by improvements in asthma control that lead to reduced exacerbations during pregnancy.

### **BARRIERS TO GOOD ASTHMA MANAGEMENT IN PREGNANCY: DEBUNKING THE MYTHS AND ADDRESSING NEGATIVE HEALTH BEHAVIORS**

#### ***Do Women Stop Using Asthma Medications While Pregnant?***

There is a large body of evidence indicating that pregnant women reduce their use of asthma medications during pregnancy, against the advice of current guidelines or their physician.<sup>28,56,128–130</sup> A 2003 survey of more than 500 women of child-bearing age who had asthma indicated that 82% of those who used ICS treatment were concerned about the effects of this medication on the fetus.<sup>131</sup> Despite also having concerns for their own health about the consequences of discontinuing medication, 36% reported that they would discontinue medication use while pregnant, without first seeking advice from their physician.<sup>131</sup>

Recent North American studies using data from prescription databases have confirmed this practice, identifying a significant decrease in prescriptions for asthma medications in early pregnancy as compared with before pregnancy.<sup>32,112,132</sup> When examining the use of asthma medications in the 6 months before and 6 months after the first pregnancy claim in a medical insurance database, Schatz and Leibman<sup>32</sup> demonstrated that of the 16% of women who used ICS before pregnancy, 52% discontinued ICS after pregnancy. The use of SABA was also discontinued in 57% of subjects using them before pregnancy.<sup>32</sup> Another American study found a 13% reduction in prescriptions for SABA, a 23% reduction in ICS, and a 54% reduction in prescriptions for oral steroids compared with the 20 weeks before pregnancy.<sup>132</sup> Blais and colleagues<sup>112</sup> also found that whereas 47.2% of women filled prescriptions for ICS before pregnancy, only 40% did in the first trimester. It is not clear whether these changes reflect changes in the attitudes of pregnant women themselves or to altered prescribing practices of their physicians.

One study did provide evidence of altered treatment of pregnant women with asthma by physicians during emergency department visits. Despite having symptoms and lung function similar to those in a nonpregnant group of women, those who were pregnant were significantly less likely to be treated with oral steroids either in the emergency department or after discharge from hospital.<sup>133</sup> The 2004 clinical guidelines for the treatment of asthma during pregnancy contain

clear messages about the safety of medication use (particularly ICS and  $\beta_2$ -agonists) during pregnancy and the importance of vigorous treatment of asthma exacerbations,<sup>28</sup> which may facilitate improvements in the outcome for both mother and baby.

Cessation of medication during pregnancy may have adverse consequences for both mother and baby. The number of emergency department or physician visits for asthma was increased among women who had not taken ICS medication before pregnancy.<sup>32</sup> Conversely, among women who were using ICS before pregnancy, there was a 36% decrease in the number of asthma-related physician visits during pregnancy. It has also been shown that women who did not use ICS during pregnancy are at greater risk of exacerbations.<sup>21</sup> Women who reduced the intensity of their asthma treatment during pregnancy (eg, from ICS use to SABA use) had babies with lower mean birth weight, birth length, and gestational age, compared with women who increased the intensity of asthma treatment during pregnancy.<sup>85</sup> A recent large prospective cohort study found that women who used less medication than was recommended by guidelines for their prepregnancy level of severity had more severe asthma during pregnancy than women who did follow the recommendations of the guidelines.<sup>14</sup> Maintaining good asthma control with appropriate

treatments is important for both maternal and fetal health outcomes.

### ***Do Women with Asthma Smoke While Pregnant?***

Many cohort studies from around the world have shown that cigarette smoking is more common among pregnant women with asthma than in pregnant women without asthma (**Table 3**).<sup>5,38,61,62,66,74,75,83,134,135</sup> There is even some evidence that smoking rates are higher still among women who do not use medication to treat their asthma.<sup>4,75,112,136</sup> A cohort study of 725 pregnant women identified maternal asthma as a predictor of pregnancy-associated smoking,<sup>137</sup> and another study showed that pregnant smokers were 4 times more likely to have asthma.<sup>138</sup> In a recent Australian study, 34% of pregnant women with asthma were current smokers, and asthmatic women were more likely to be heavier smokers than pregnant women without asthma.<sup>5</sup> Higher rates of passive smoke exposure among pregnant women with asthma (24%) compared with nonasthmatic women (4%) have also been described, but were not significant when considering only the subgroup of nonsmoking women.<sup>66</sup> Recently, a North American analysis of more than 2000 pregnant women with asthma found that 36% of nonsmokers were exposed to passive smoke at home.<sup>139</sup>

**Table 3**  
Cigarette smoking among pregnant women with and without asthma

Study	Country	% Smokers in Asthma Group (%)	% Smokers in No-Asthma Group (%)
Dombrowski et al, <sup>134</sup> 1986	USA	46	28
Stenius-Aarniala et al, <sup>25</sup> 1988	Finland	8.8	16.2
Stenius-Aarniala et al, <sup>21</sup> 1996	Finland	11.5	15.2
Alexander et al, <sup>75</sup> 1998	Canada	34.8	27.3
Minerbi-Codish et al, <sup>38</sup> 1998	Israel	16.8	6.5
Demissie et al, <sup>61</sup> 1998	USA	15.3	12.1
Kurinczuk et al, <sup>135</sup> 1999	Australia	25.3	22.3
Mihrshahi et al, <sup>66</sup> 2003	Australia	30	17
Sheiner et al, <sup>83</sup> 2005	Israel	11.1	4.2
Clark et al, <sup>4</sup> 2007	UK	36.1	36.1
Kallen and Otterblad Olausson, <sup>62</sup> 2007	Sweden	16.3	12.4
Tata et al, <sup>74</sup> 2007	UK	34.3	31.0
Bakhireva et al, <sup>136</sup> 2007	USA and Canada	11.5	8.3
Enriquez et al, <sup>17</sup> 2007	USA	38	27.5
Clifton et al, <sup>5</sup> 2009	Australia	34	28
Murphy et al, <sup>140</sup> 2010	Australia	34	15

In pregnant women with asthma, current and former smokers had higher rates of severe exacerbation than never smokers, and these exacerbations were more severe in current smokers as demonstrated by higher asthma control scores.<sup>140</sup> Another study showed a greater number of symptomatic days and nights of sleep disturbance among active smokers than in nonsmokers with asthma.<sup>139</sup> Smoking is a well-recognized contributor to poor perinatal outcomes. Although the combined effects of maternal smoking and asthma have not been systematically investigated, both smoking and exacerbations are risk factors for low birth weight, so it is possible that smoking further increases the perinatal risks associated with asthma.<sup>139</sup> Smoking cessation programs should be provided to all pregnant women, and particularly those with asthma, and avoidance of triggers, including passive smoke exposure, should be strongly encouraged.<sup>28,141</sup>

### ***Is There Any Relationship Between Asthma in Pregnancy and Anxiety and Depression?***

Asthmatic women have a 52% increased risk of suffering depression during pregnancy compared with women without asthma,<sup>74</sup> which is not dependent on medications and was further elevated (twofold increased risk) among women who had exacerbations of asthma during pregnancy.<sup>74</sup> There has also been an increased use of antidepressants reported among women using antiasthmatic drugs during pregnancy.<sup>62</sup>

Psychological stress and anxiety may contribute to worsening of asthma in nonpregnant adults. Among university students, sputum eosinophils following allergen challenge are increased in the final examination week (characterized by significantly higher depression and anxiety scores) compared with mid-semester,<sup>142</sup> demonstrating an interaction between psychological stress and deteriorating airway inflammation in asthma.

Stress, anxiety, and depression may be contributors to worsening asthma during pregnancy. Concerns about the effects of medication use on the baby appear to lead to anxiety and nonadherence among pregnant women with asthma.<sup>128,131</sup> One survey reported that 5% of women with asthma reported feeling sadness, depression, or anxiety, 44% were worried for the baby, 11% were concerned that their stress and worry could lead to asthma attacks, and 7% were fearful of having an asthma attack in public.<sup>128</sup> A randomized controlled trial has demonstrated a potential benefit of relaxation techniques among pregnant women with asthma.<sup>143</sup> Over an 8-week period, there was a significant improvement in FEV<sub>1</sub>

(forced expiratory volume in 1 second) among women with asthma who received training in progressive muscle relaxation, compared with women trained in sham exercise. Other benefits of this therapy included an improvement in health-related quality of life and a reduction of anger levels.<sup>143</sup> Improving psychological parameters may have significant effects on lung function during pregnancy.

### **EFFECTIVE TREATMENT AND MANAGEMENT OF PREGNANT WOMEN WITH ASTHMA**

Asthma that is well controlled in pregnancy is less likely to result in adverse outcomes than poorly controlled asthma. Consequently, during pregnancy regular medical review and monitoring of asthma is recommended, and a multidisciplinary approach may be most effective. The goals of management in pregnant women are to minimize asthma symptoms and limitations, prevent exacerbations, and maintain near normal lung function with minimal medication use, thereby ensuring maternal quality of life and normal fetal maturation.<sup>28</sup>

### ***What is the Safety Level of Asthma Treatments in Pregnancy?***

In 2004, the National Asthma Education and Prevention Program (NAEPP) released an updated expert panel report on the management of asthma in pregnant women.<sup>28</sup> This report addressed safety concerns of asthma medications in pregnancy, and found that there was a significant amount of reassuring data on the safety of SABA, particularly albuterol.<sup>28</sup> A prospective cohort study found no significant differences in perinatal mortality, congenital malformations, preterm delivery, and low birth weight in asthmatic women who used SABA compared with women who did not use treatment for asthma during pregnancy.<sup>99,144</sup> There are limited data available on the use of long-acting  $\beta_2$ -agonists (LABA) during pregnancy. An epidemiologic study reported no adverse outcomes among 65 women who used salmeterol while pregnant.<sup>145</sup> Current guidelines recommend salmeterol as the preferred LABA used in pregnancy, based on its having been available for a longer period of time in the United States.<sup>28</sup>

The majority of studies addressing the safety of ICS use in pregnancy have examined women using budesonide and consequently, this is the ICS of choice, recommended for use in pregnant women with persistent asthma, following a step-wise approach to achieve asthma control.<sup>28</sup> However, because other ICS drugs have not

been shown to be unsafe, women whose asthma was well controlled on other medications could continue to use these during pregnancy.<sup>28,146</sup>

The use of ICS medication for asthma during pregnancy in appropriate doses does not appear to result in any adverse outcomes for the fetus<sup>99</sup>; and although many studies in this area have lacked statistical power,<sup>147</sup> a meta-analysis of recent data (1997–2005) examining the relationship with perinatal outcomes provided further reassurance.<sup>148</sup> By maintaining adequate asthma control, ICS use may actually protect against some adverse outcomes such as low birth weight.<sup>32,89</sup> An adequately powered, large multicenter prospective cohort study found no significant relationships between ICS use during pregnancy and outcomes such as preterm birth at less than 32 weeks' gestation, major malformations, low birth weight, and small for gestational age infants.<sup>99</sup>

Most data on asthma treatment during pregnancy are derived from cohort studies. However, one randomized controlled trial of low-dose budesonide (400 µg/d) versus placebo among patients with recent-onset mild to moderate asthma included a subgroup of 313 pregnant women.<sup>120</sup> The rate of adverse pregnancy outcomes (including spontaneous abortion, neonatal death, and congenital abnormalities) was similar among women using low-dose budesonide or placebo throughout pregnancy. Unfortunately, other important perinatal outcomes such as birth weight were not reported in this study.<sup>120</sup>

Estimates suggest that approximately 2.4% of pregnant women with asthma use oral corticosteroids at some time during pregnancy.<sup>62</sup> The effects of oral steroid use on pregnancy are not well described, due to a lack of information about doses, timing, and length of use. Associations between oral steroid use and preeclampsia,<sup>76,149</sup> preterm delivery,<sup>72,86,99</sup> and reduced birth weight<sup>26,99</sup> have been described. However, it is difficult to separate the effects of the drug from the effects of the exacerbations that necessitated its use. A recent study of more than 113 pregnant women with asthma who used systemic steroids during pregnancy has addressed this question with linear regression analysis, finding that oral steroid use was significantly associated with birth weight, whereas all measures of asthma control (including hospitalizations) were not significantly associated with birth weight.<sup>26</sup>

Asthma should be well managed to avoid the need for rescue oral steroid medication.<sup>146</sup> However, when required for the treatment of a severe exacerbation during pregnancy, the possible risks described are still less than the risks

of severely uncontrolled asthma, which may result in maternal and/or fetal death.<sup>28,146</sup>

Information on the safety of leukotriene receptor antagonists (LTRAs) for asthma during pregnancy is limited.<sup>136,150</sup> In one study of 96 women using LTRAs, no increased risk for preterm delivery, gestational diabetes, preeclampsia, or pregnancy loss was found, compared with 122 women with asthma who used SABA.<sup>136</sup> However, there was a small decrease in birth weight among users of LTRAs, and an increase in the prevalence of major structural anomalies compared with a nonasthmatic group, albeit among a small sample size.<sup>136</sup> Sarkar and colleagues<sup>150</sup> also found a decrease in mean birth weight among users of LTRAs. Current guidelines do not specifically recommend the use of LTRAs during pregnancy, due to the limited data available, unless the woman's asthma was previously well controlled on these medications before pregnancy.<sup>28</sup>

### ***How Should Exacerbations be Treated in Pregnancy?***

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Women with asthma should receive vigorous treatment of an exacerbation during pregnancy to reduce the risk of readmission and to improve outcomes for the fetus.<sup>28</sup> At least one study has found that pregnant women were significantly less likely to be prescribed oral steroids, either in the emergency department or on discharge from hospital, compared with nonpregnant women.<sup>133</sup> Following discharge from hospital, the pregnant women were 3 times more likely to report an ongoing asthma exacerbation than the nonpregnant women.<sup>133</sup> Another study found that hospitalizations were more common during pregnancy than before pregnancy, and emergency department presentations and oral steroid courses were less likely during pregnancy than before pregnancy,<sup>19</sup> suggesting either that treatment approaches differ in pregnancy or there are changes in the frequency or severity of exacerbations during pregnancy.<sup>19</sup> A severe asthma attack presents more of a risk to the fetus than the use of asthma medications because of the potential for fetal hypoxia, so therapy should be maximized during any asthma exacerbation which occurs.<sup>28</sup> Management of an asthma emergency during pregnancy should involve cooperation between the respiratory specialist and obstetrician, to achieve close monitoring of lung function and fetal activity as well as maintenance of oxygen saturation above 95%.<sup>28</sup>

Two randomized controlled trials of asthma therapy during pregnancy have addressed treatment of exacerbations as well as treatment to

prevent exacerbations. Wendel and colleagues<sup>151</sup> studied 84 women with 105 exacerbations during pregnancy, who were randomized to receive methylprednisolone with intravenous aminophylline or methylprednisolone alone at the time of admission to hospital. Although women receiving aminophylline reported more side effects, there was no difference in length of hospital stay between treatments.<sup>151</sup> The women were further randomized on discharge to receive inhaled  $\beta_2$ -agonist with either oral steroid taper alone or ICS (beclomethasone) plus oral steroid taper. The re-admission rate was reduced by 55% with the inclusion of ICS on discharge.<sup>151</sup>

The second trial compared the use of inhaled beclomethasone and oral theophylline for the prevention of asthma exacerbations during pregnancy in women with moderate asthma.<sup>152</sup> There was no difference in the rate of severe exacerbation between groups nor in perinatal outcomes.<sup>152</sup> Inhaled beclomethasone was a suitable alternative to theophylline for asthma treatment during pregnancy, but did not reduce the exacerbation rate. Other studies have described a reduction in exacerbations with the use of ICS medication,<sup>21,32</sup> emphasizing the importance of women using appropriate preventive medication for asthma control during pregnancy.

### ***How Should Asthma Management be Approached in Pregnancy?***

While most women with asthma have disease of mild severity,<sup>91</sup> changes in disease status are to be expected during pregnancy. The NAEPP report indicates that individual treatment plans are required to address specific circumstances and patient needs, and that self-management of asthma is an important component of overall management.<sup>28</sup> It is important that changes in lung function and asthma control are detected early. Women should receive education about the use of regular peak flow monitoring at home, and they should be provided with a written asthma action plan outlining how to respond to changes in their asthma and when to seek medical advice.<sup>28,153</sup>

An Australian study found that pregnant women with asthma have poor asthma skills and knowledge.<sup>141</sup> At the beginning of pregnancy, 40% of women self-reported nonadherence to ICS medication, 16% had inadequate inhaler technique, and 42% had inadequate knowledge about their asthma medications.<sup>141</sup> Regular peak flow monitoring was performed by 3%, and 15% had a written action plan.<sup>141</sup> Asthma self-management education during pregnancy was subsequently provided in an antenatal clinic

**Table 4**  
**Structured clinical assessment of asthma during pregnancy**

1. Asthma control	Symptoms	Type (dyspnea, wheeze, cough, chest tightness) Pattern (response to triggers and treatment, intensity, frequency) Timing (nocturnal, on waking, with exercise)
	Lung function	Airflow limitation
2. Exacerbations	Frequency Severity	
3. Asthma skills	Inhalation device selection and technique Asthma knowledge Self-monitoring Adherence Written action plan	
4. Asthma treatment	Compare with recommendations Optimize ICS dose Step up treatment category according to guidelines	
5. Asthma triggers and comorbidities	Identify Avoidance strategies	Comorbidities (rhinitis, gastroesophageal reflux, obesity)

setting, contributing to an improvement in skills among pregnant women. During the 30- to 60-minute session with an asthma educator, women received education about asthma control and assessment of management skills, including trigger avoidance, smoking cessation, inhaler technique, and medication adherence. Women assessed as unstable and requiring medical review were referred to their primary care physician or to a respiratory physician for review. An individualized written action plan was provided. Asthma education during pregnancy was associated with significant improvements in all aspects of self-management as well as a significant increase in ICS use in women with moderate and severe asthma.<sup>141</sup> Women with severe asthma also reported fewer nighttime asthma symptoms and less use of reliever medications after receiving education.<sup>141</sup>

Pregnant women with asthma have a need for further education, information, and self-management skills.<sup>128</sup> An outline of a structured clinical assessment of asthma during pregnancy is given in **Table 4**. Few women report discussing their concerns about medications with their physician.<sup>131</sup> A multidisciplinary approach to prenatal and asthma care may benefit pregnant women, and is recommended.<sup>28</sup> Chambers<sup>131</sup> found that 40% of women would continue using ICS medication solely on the recommendation of their obstetrician. Recent studies have proposed that nurses and midwives have key roles to play in educating pregnant women with asthma, in culturally sensitive ways, which will empower them to alter their behavior and make lifestyle changes that control asthma symptoms.<sup>104,154</sup> Significant deficiencies in asthma knowledge and self-management skills among pregnant women might be greatly improved by asthma education, potentially leading to better asthma control and improved fetal outcomes.

## SUMMARY

Asthma is a highly prevalent medical problem during pregnancy. Exacerbations of asthma or poorly controlled disease can increase the risk of adverse perinatal outcomes, which may influence future health. Well-controlled asthma during pregnancy is not considered to be a significant risk to the baby, and regular monitoring of maternal asthma throughout pregnancy is recommended. By controlling asthma and preventing severe exacerbation, ICS may provide protection against adverse outcomes. Improvements in asthma management that address health behavior issues such as maternal smoking, poor

self-management skills, and nonadherence to medication will be important in improving perinatal outcomes for women with asthma.

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