

The Change of Asthma Course During Pregnancy

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Abstract

The course of asthma during pregnancy is variable. When the total pregnant asthmatic population is considered, one-third improve, one-third are unchanged, and one-third experience increased symptoms. The course of asthma may be influenced by the many physiologic changes during pregnancy as well as the severity of the pre-existing asthma.

Prospective studies have found that severe asthmatics have exacerbations during pregnancy more often than mild asthmatics. The first trimester and the last month of pregnancy are relatively free of exacerbations. The second and third trimesters have more potential for increased asthma symptoms and the need for medications. Change in allergic nasal symptoms may precede similar changes in asthma during pregnancy. The course of asthma during labor and delivery is worsened in only 10% of patients, and their problems are usually mild. Postpartum most women return to their prepregnant state within 3 mo.

Physiologic changes in pregnancy affect the pulmonary function with a decrease in functional residual capacity (FRC) and 50% increase in minute ventilation. This change results in hyperventilation in 60–70% of normal pregnancies and a sensation of dyspnea that can be distressing to an asthmatic. There is also nasal congestion in 22–72% of pregnancies beginning in the second trimester, which can also affect asthma. The gastrointestinal system is affected in pregnancy with one-third of women having gastroesophageal reflux disease (GERD).

Undertreatment of asthma during pregnancy remains a problem in emergency departments. With awareness of the patient's prepregnant state, careful monitoring during pregnancy will prevent serious exacerbations and complications.

Index Entries

Asthma; pregnancy; pregnant; exacerbation; severity; postpartum.

Change of Asthma Course During Pregnancy

Bronchial asthma is a chronic disease in which incidence and mortality increased by more than 30% in the 1980s (1). The course of bronchial asthma is one of exacerbation and remission caused by a cascade of events. Airway inflammation (with infiltration of inflammatory cells such as eosinophils, lymphocytes, and mast cells) leads to increased airway responsiveness and airway obstruction. There are multiple intrinsic and extrinsic factors that can influence the course of asthma, all of which can occur concomitantly with pregnancy.

Asthma is the most common chronic pulmonary disease that complicates approx 4% of all pregnancies (2). This percentage is most likely an underestimate because in many mild cases, similarly to the general population, asthma is undiagnosed. The effect of pregnancy itself on asthma has been evaluated in many studies over the years. The general conclusion by Juniper and Newhouse (3), who used meta-analysis to evaluate both retrospective and prospective studies, is that one-third of women show improvement of asthma during pregnancy, one-third experience no change, and one-third experience a worsening of their asthma. Great variations occur among the individual studies, which may be the result of the way asthma was assessed and the source of the populations studied (i.e., prenatal or pulmonary clinics influencing the severity of asthma existing pre-pregnancy). Historically, it is important to recall that for many years, both obstetricians and their patients would stop all treatment as soon as pregnancy began. Asthma was not regarded as a high-risk condition, thus it is likely that more women had severe difficulty with their asthma before being treated. In *William's Obstetrics* 1966 (4), the entire subject of asthma and pregnancy is discussed in just two paragraphs. Relying on one retrospective study (5), it states that pregnancy had no effect on asthma in the majority of cases. No mention

is made of any specific problems with asthma during pregnancy or any specific treatment.

Normal Physiologic Changes of Pregnancy

There are many physiologic changes that occur during pregnancy. Some of these may have beneficial effects on the course of asthma and others may be deleterious (Table 1) (6).

Respiratory Tract

The impact on the respiratory tract during pregnancy is both physical and functional. The diaphragm rises about 4 cm, the transverse diameter of the thoracic cage increases about 2 cm, and thoracic circumference increases about 6 cm. Diaphragmatic excursion is greater during pregnancy, but there is still a significant reduction in expiratory reserve volume and residual volume of air in the lungs, especially in the last trimester. By term, there is a 17–25% decrease in functional residual capacity (7).

The respiratory rate is only slightly changed during pregnancy, but the tidal volume, minute ventilatory volume, and minute oxygen uptake increase substantially by the last trimester (Table 2) (8,9). The most consistent respiratory change is an increase of almost 50% in minute ventilation, which is caused by respiratory center stimulation from increasing concentrations of progesterone (10). Oxygen consumption also rises 21–35% but peaks later in pregnancy than the rise in minute ventilation (11).

Lung compliance, total lung capacity, vital capacity (VC), and forced expiratory volume in 1 s (FEV₁) are unaffected by normal pregnancy. Total pulmonary resistance is reduced and airway conductance is increased, most likely because of the action of progesterone. The closing volume (lung volume at which dependent airways begin to close during expiration) may also be higher during pregnancy (12).

Hyperventilation occurs in 60–70% of pregnant women, especially in the first and second trimesters. The mechanism of this dyspnea is

Table 1
Physiologic Changes During Pregnancy That May Affect the Course of Asthma

Factors That May Improve Asthma

- Progesterone-mediated bronchodilation
- Decreased plasma-histamine-mediated bronchoconstriction (resulting from increased circulating histaminase)
- Estrogen- or progesterone-mediated potentiation of β -adrenergic bronchodilation
- Pulmonary effects of increased serum-free cortisol
- Glucocorticosteroid-mediated increased β -adrenergic responsiveness
- Prostaglandin I₂-mediated bronchial stabilization
- Atrial natriuretic factor-induced bronchodilation
- Increased half-life or decreased protein binding of endogenous or exogenous bronchodilators
- Prostaglandin E-mediated bronchodilation (in the last 4 wk)
- Descent of fetus (during the last 4 wk)

Factors That May Worsen Asthma

- Pulmonary refractoriness to cortisol effects because of competitive binding to glucocorticosteroid receptors by progesterone, aldosterone, or deoxycorticosterone
- Prostaglandin F₂ α -mediated bronchoconstriction
- Decreased FRC with resultant airway closure during tidal breathing and altered ventilation: perfusion ratios
- Increased pulmonary capillary permeability
- Increased upper airway resistance from nasal turbinate congestion
- Increased placental major basic protein reaching the lung
- Increased viral or bacterial respiratory infections triggering asthma exacerbations
- Increased gastroesophageal reflux-induced asthma
- Increased stress
- Elevation of the diaphragm from the expanding uterus (in second and third trimesters)

Modified from ref. 6.

thought to be the increase in tidal volume that lowers the blood Pco₂ and results in increased respiratory effort induced by both progesterone and estrogen.

Although pulmonary function is not impaired in normal pregnant women, the sensation of dyspnea may cause apprehension and subsequent exacerbation in pregnant asthmatics.

Table 2
Pulmonary Function in Pregnancy and Postpartum

Function	10 wk	24 wk	36 wk	pp
Respiratory rate	15–16	16	16–17	16–17
Tidal volume	600–650	650	700	550*
Minute ventilation	—	—	10.5	550*
Vital capacity	3.8	3.9	4.1	3.8
Residual volume	1.2	1.1	1.0	1.2*

*Significant difference compared to pregnant women.

The decreased pulmonary reserve and increased respiratory effort may also cause increased asthma.

The upper respiratory tract is also affected in pregnancy. Marked congestion of the inferior nasal turbinates (stuffy nose of pregnancy) lasting at least 10 d and not caused by viral infection or allergy has been reported to occur in 22–72% of all pregnancies (13,14). Ellegard (13) noted that symptoms began most often during weeks 20–22 of gestation. Nearly all women show improvement by 2–4 wk postpartum.

A prospective study of 568 pregnant asthmatics showed a significant correlation between the course of gestational asthma and the course of rhinitis during pregnancy. In those patients who reported that their asthma improved dur-

ing pregnancy, 51% also showed improved rhinitis symptoms and 20% experienced increased rhinitis. Only 2% of patients whose asthma worsened reported improved rhinitis, and 56% said their rhinitis was worse (15). In patients whose asthma did not change through the course of pregnancy, 27.5% also noted an increase in rhinitis.

Hormonal Changes

There are marked changes in estrogen and progesterone levels during pregnancy. Progesterone is elevated and stable through the first trimester; then levels rise to 900% higher by term. Estrogen levels also rise throughout pregnancy to 100 times more estradiol and 1000 times more estriol at term. Progesterone levels decrease sharply immediately before delivery, increasing uterine contractility.

Elevated progesterone reduces coordinated contractility in the smooth muscle of the uterus by inhibiting the formation of gap junctions (16). It has not been shown that progesterone has a similar effect on the pulmonary smooth muscle. However, the lowest rates of symptoms in asthmatics occur in the last 4 wk of pregnancy with reduced wheezing, sleep interference, and activity interference (17).

Both β -estradiol and progesterone combine to enhance peripheral eosinophil degranulation in vitro in cells from patients with allergic rhinitis (18). There is an increase in free cortisol starting early in pregnancy and reaching 2.5 times nonpregnant levels by the third trimester. Similar amounts of free cortisol in nonpregnant volunteers have been shown to decrease circulating monocytes and T cells.

Gastroesophageal Reflux

In asthma, reflux is associated with disease exacerbation. Medical and surgical treatment of reflux has resulted in a decrease in asthma symptoms. The increase in serum progesterone during pregnancy causes relaxation of the smooth muscle in the lower esophageal sphinc-

ter, resulting in reflux, heartburn, and indigestion in one-third of all pregnancies (19,20).

Studies of Asthma Course During Pregnancy

Retrospective Studies

The changes in asthma symptoms during pregnancy have been reported in several retrospective (mostly case) studies from 1930 to 1967 (5,21–28). In these studies of 25 or more women, comprising 1087 pregnancies. Of these, 36% improved, 41% were unchanged, and 23% worsened during pregnancy (7).

There was a marked difference in results from different investigators (Table 3). The beneficial effect of pregnancy on asthma ranged from 3 to 50%. There was no effect in 15–93%, and an adverse effect was reported in 4–54% of patients. These subjects were found either by chart review (23,25,27,28) or by interview up to several years after their pregnancies (5,21,22). The changes in the course of asthma were determined by reviewing medication requirements, symptoms, and hospitalizations.

Patients studied by Jensen (21), Gandevia (22), Gammal (25), Hiddlestone (28), and Williams (27) came from asthma or allergy clinics. These may have been biased toward women with more problematic asthma and fewer mild asthmatics. Jensen (21) excluded 22 of a potential 106 women because their allergic disease was quiescent during pregnancy. Because these patients came from asthma clinics, their diagnosis probably was correct. The course of asthma during pregnancy was assessed through changes in their medications. Asthma was said to be worse if medication use increased and improved if medication use decreased. Over time, asthma treatment has changed. Medications in the past would not have included inhaled steroids, which are a mainstay of treatment today. Thus, evaluation of older studies are not comparable to more recent series.

Other retrospective studies included patients from obstetrical (5) or general clinics (23).

Table 3
Effect of Pregnancy on Asthma

Name of first author	Retrospective Studies		
	Improved (%)	Same (%)	Worse (%)
Jensen (Denmark)	41	15	44
Gandevia (Australia)	48	28	24
Turiaf (France)	50	26	24
Schaefer (United States)	3	93	4
Gammal (Egypt)	35	25	40
Hiddlestone (New Zealand)	39	35	27
Williams (UK)	42	34	24
Williamson (United States)	20	36	54
Fein (United States)	10	67	23
Average	36	41	23

From ref. 7 with permission.

These women generally were not comanaged with an asthma specialist. Some of these patients could have been misdiagnosed. In addition, the use of appropriate asthma medication was less likely.

The severity of asthma before or after pregnancy was not noted in any of these studies. Pulmonary function testing as an objective measure was not always available; therefore, physicians' and patients' clinical assessments were necessary to evaluate changes in the course of asthma. The course of asthma during pregnancy from these early studies is variable. Local environmental conditions are not a factor because of similar data from different locations.

Prospective Studies

Since 1976, several studies have prospectively looked at the course of asthma during pregnancy. At that time, the latest edition of *William's Obstetrics* advised that "most drugs that have proved effective before pregnancy may be continued during pregnancy." In pregnant patients, undertreatment of asthma resulting from fears of adverse effects to the fetus continued to be a major problem, especially among obstetricians. Most patients were enrolled from maternity clinics and followed through deliv-

ery and into postpartum (7,14,17,29,30). One study enrolled patients from an asthma clinic before pregnancy (31). The criteria for entry in the studies was a past or present history of asthma. Three studies included a control cohort of pregnant nonasthmatic women, which is more helpful in assessing the effect of asthma on pregnancy. Patients reported their prepregnant condition and many were followed postpartum, which served as another control. Again, when the total population of asthmatics were followed, about one-third were improved, one-third were unchanged, and one-third worsened (Table 4).

Five prospective studies followed the course of asthma through pregnancy. Of those, four stratified their subjects according to the severity of asthma at the beginning of pregnancy (7,29–31).

Gluck and Gluck (7) followed all patients with a history of asthma (past or present) from their first visit to a prenatal clinic. Patients were stratified by severity of asthma based on frequency of symptoms before pregnancy. Severe asthmatics (12 patients) had symptoms at least weekly. Moderate asthmatics (10 patients) had attacks at least monthly but not as frequently as the severe group. Those with symptoms less often than monthly but with a history of one or

Table 4
Effect of Pregnancy on Asthma: Prospective Studies

First author	No.	Improved (%)	Same (%)	Worse (%)
Gluck and Gluck	47	14	43	43
Schatz	330	28	33	35
Stenius-Aarniala	198	18	40	42
White	31	69	22	9
Juniper	16	50	37.5	12.5
Average	622	36	35	28

From ref. 7 with permission.

more attacks within the preceding 5 yr were considered mild asthmatics (25 patients).

In contrast, Stenius-Aarniala and Asso (29) divided their patients by severity based on medication requirements and clinical course during pregnancy (Table 5). White et al. (30) stratified a group of 31 patients at the time of entry based on medication usage. Mild asthmatics required only occasional bronchodilators, moderate asthmatics used bronchodilators more than half of the days and/or required inhaled steroids, and severe asthmatics required oral steroids. Only one was considered severe and more than half (17 of 31) were mild.

Juniper et al. (31) divided patients based on medications required to control asthma symptoms. She used statistical analysis based not only on the class of drug and dosage but also methacholine challenge. There were 5 mild, 1 moderate, and 10 severe patients with asthma in this study. The clinical course of asthma during pregnancy was assessed for the group overall. Eight patients improved, six were unchanged, and two deteriorated. In addition, using the methacholine challenge, Juniper documented objective changes during pregnancy.

Because the course of asthma during pregnancy is related to the severity of asthma (discussed later), variations in findings can be attributed to the different proportions of the asthma subgroups. In the two studies with a similar distribution of asthmatics (7,29) the results were the same.

Course of Asthma During Pregnancy

By Severity

When the course of asthma was examined in patients with mild asthma and occasional wheezing and bronchodilator usage, the majority showed no change in their disease. Gluck and Gluck (7) found 16% of mild asthmatics were worse during pregnancy, 12% improved, and 72% were unchanged. Stenius-Aarniala (29) found that 22% of mild asthmatics were worse during pregnancy and improved after delivery. The patients in White's study (30) were of mild or moderate severity at the start of pregnancy; the majority of patients improved or had no change in severity. Improvement was noted especially in the third trimester in peak flow measurements and perception of asthma symptoms. Thus, it appears that patients with mild or moderate asthma before pregnancy are not usually exacerbated during pregnancy.

When severe asthmatics were evaluated, a different picture emerged. Gluck and Gluck (7) found that none of their severe asthmatics improved during pregnancy, 17% were unchanged, and 83% worsened, with 9 hospitalizations for status asthmaticus in 12 patients. In the larger study by Stenius-Aarniala (29), the most severe asthmatics had significantly lower FEV1 and maximum flow at 50% VC during the last month of pregnancy. When surveyed postpartum, 34.5% of all patients felt their asthma was better than during preg-

Table 5
Classification of Asthma Severity During Pregnancy

Type of asthma (no.)	Medication	Exacerbation	Hospitalization
Very mild (56)	None or inhaled bronchodilators, Na cromolyn, or beclomethasone	None	None
Mild (52)	As above, plus oral bronchodilator	None	None
Moderate (56)	As above	One or more	None
Severe (34)	As above	One or more	One or more

Adapted from ref. 29.

nancy. Most of the severe patients (56%) were better after delivery. These studies show that the course of asthma in pregnancy varies with the severity of asthma prior to pregnancy. Severe asthmatics tend to have exacerbated disease with more symptoms and require more medications than women with a milder form of disease.

By Stage of Pregnancy

All stages of pregnancy are not the same; the first trimester is well tolerated in asthmatics with only rare exacerbations (7,17,30,31). Gluck and Gluck found increased symptoms did not occur before the fourth month of gestation and the peak occurred during the sixth month regardless of the severity of the asthma. Schatz (17) found an increase in symptoms between 29 and 36 wk gestation in those women whose asthma was worse during pregnancy. Juniper (31) also found an increase in symptoms in the second and third trimesters compared to preconception in 5 of 16 patients. Using methacholine challenge, objective changes were documented during pregnancy, showing improvement in the second trimester (31). Stenius-Aarniala (29) found that most acute exacerbation occurred between 17 and 24 wk (19).

In the last month of pregnancy, asthma improves (17) in many mild to moderate asthmatics. Stenius-Aarniala (29) found lower FEV₁ in patients with severe asthma in the last month of pregnancy, but patients were less likely to have exacerbations at this time. Schatz et al. (17) assessed asthma symptoms at 4-wk intervals throughout pregnancy and found both

fewer and less severe symptoms in the last 4 wk of pregnancy than any other interval. Even among women whose asthma worsened during pregnancy, there was relative improvement in the last 4 wk (15).

These studies suggest that the first trimester and the last month of pregnancy are relatively free of exacerbations and that the second and third trimesters have more potential for increased asthma symptoms.

In Labor and Delivery

About 10% of asthmatics will have increased symptoms during labor and delivery. These symptoms are usually mild and easily controlled (29). In one study of 360 patients, 37 patients were symptomatic during labor and delivery. Of these 37, 54% required no treatment, 15% used inhaled bronchodilators, and 5% were given intravenous aminophylline (17). Mabie et al. (32) reported an 18-fold increased risk of exacerbation with cesarean section compared to vaginal delivery.

Postpartum

In general after delivery, asthma returns to the severity that was present before pregnancy. Whereas the course of asthma during pregnancy was unchanged, the disease remained the same after delivery in 72% of women studied. When asthma changed during pregnancy, it returned to prepregnancy state in 74% of women within 3 mo (17). Of women with severe asthma during pregnancy, 56% had fewer symptoms after delivery, whereas only 22% of mild asthmatics improved after giving birth (29).

These data support the concept that the changes in the course of asthma during pregnancy are more than just random fluctuations in the natural course of asthma. Several other studies observed that asthma changes that occurred during pregnancy reverted to the prepregnancy state within 3 mo after delivery (7,21,22,30,31).

Course of Asthma in Subsequent Pregnancy

Several studies have found that the course of asthma is similar for subsequent pregnancies. Gammal (25) reported consistency in deterioration in 29 of 33 patients and consistent improvement in 23 of 28 patients. Williams (27) found 63% of his patients had similar course and all of Jensen's patients (21) were consistent. Stenius-Aarnalia followed 13 women through two pregnancies but adjusted medications at an earlier stage in the second pregnancy; this led to better asthma control. Schatz (17) noted exact concordance in the course of asthma in 58.8% of 34 women seen through two pregnancies.

Other Factors Affecting Asthma During Pregnancy

Reluctance to Treat

Asthma severity is an important risk factor during pregnancy, as is control of asthma. There are factors, such as reluctance to treat, that will result in poor control of asthma during pregnancy. Additionally, there is decreased compliance because of patient concerns about the safety of medication for the fetus.

A study of treatment of acute asthma in emergency departments across the United States included 551 women (51 pregnant and 500 not pregnant) (33). Both groups had similar duration of symptoms and peak expiratory flow rates (51%). However, there was a significant difference in treatment. Pregnant women were less likely to be given systemic corticosteroids (44 vs 66%) in the emergency department. This decrease was not because of concern about ste-

roid exposure in the first trimester because corticosteroids were used almost equally in all trimesters: 53, 40, and 50% during the first, second, third trimesters, respectively. Among those patients who were admitted, pregnant women had lower final peak expiratory flow rate (PEFR) in the emergency department and had longer hospital stays (3 vs 2 d). On discharge from the emergency department, pregnant patients were significantly less likely to be given systemic corticosteroids ($p = 0.002$). This undertreatment may partially explain continued asthma symptoms at 2 wk follow-ups in pregnant patients (three times more often than symptoms in nonpregnant patients; $p = 0.002$). Only 41% of pregnant asthmatics seen in emergency departments were on inhaled corticosteroids when they presented with severe disease, another indication of the continuing reluctance to treat asthma in pregnancy (33).

Fetal Antigenicity

The fetus is antigenically foreign to the mother. An exchange of cells between mother and fetus occurs in 10–20% of normal pregnancies. In view of this exchange, an inappropriate response to fetal antigens may provoke increased asthma (34).

In an attempt to explain the variations in response to subsequent pregnancies, 34 women who delivered both a boy and a girl were studied by retrospective questionnaires. The sex of the fetus did not affect the course of asthma. Conversely, in a prospective study, Beecroft (35) found that the women with female fetuses had more asthmatic symptoms. Because male fetuses produce a surge of androgens at weeks 12–16, gender may be a factor in this interesting observation (35). In a larger cohort, Kircher et al. (15) found no relationship between the sex of the fetus and the course of asthma.

Atopy and Allergens

Atopy can contribute to allergic symptoms and asthma when there is seasonal or environ-

mental exposure to specific allergens. Serum IgE or skin-prick tests have been used to measure atopy in pregnancy and its effect on asthma (7,31). Most asthmatic women were found to be atopic. Stenius-Aarniala (29) found that the atopic women had milder asthma with significantly fewer hospital admissions than the nonatopics. Of the women with increasing IgE throughout their pregnancy, Gluck and Gluck found that asthma either remained the same or worsened (7). In a group of inner-city women, Henderson found that worsening asthma during pregnancy was associated with increased levels of cockroach-specific IgE (36). It is difficult to determine if the atopic state is affected by the changes in the immune system during pregnancy, the season or environmental exposures, and in what way they interact.

Respiratory Tract Infections

A decrease in cell-mediated immunity makes the pregnant patient more susceptible to viral infections (37,38). It has been reported that viral infections are the most common precipitators of severe asthma during pregnancy (27). In addition, sinusitis may exacerbate asthma and has been reported to be six times more common during pregnancy (39).

Pneumonia has been found more often in asthmatic women than nonasthmatics during pregnancy. Of more than 27,500 women, 60 were identified as having pneumonia during pregnancy (40). A history of asthma was found in 37% of this group compared to a 5% history of asthma in the control group of women, with no pneumonia delivered at the same time. Those with asthma had a more than fivefold increase in the risk of developing pneumonia during pregnancy. These women were more likely to be treated for preterm labor and delivered at an earlier gestational age (40). Other studies have also found an increased history of asthma (8 vs 25%) in pregnancies complicated by pneumonia (41,42).

Smoking

Smoking is a significant risk factor in pregnancy and also exacerbates asthma. A survey in Australia of recently delivered women showed 21% had a history of asthma and 12% had active asthma. Overall, 22.7% of women smoked during pregnancy. Current asthmatics were more likely to smoke than nonasthmatics, although this difference was not statistically significant (43). A review of data collected prospectively from 568 asthmatics did not show an association between smoking and worsening of asthma during pregnancy (15). This sparing effect might explain why more asthmatics did not stop smoking during their pregnancies.

Conclusions

The course of asthma is changed by pregnancy in variable ways and for unknown reasons. Even though the prospective studies used different criteria to stratify the severity of the patient's asthma, their conclusions were remarkably similar. Overall, an equal number of women improve, are unchanged, or worsen throughout pregnancy. Asthma symptoms can worsen during pregnancy because of identifiable factors such as infection, GERD, reduction of appropriate medications by physician or patient, and smoking. Undertreatment, which is still a problem during pregnancy, leads to continued difficulty with asthma.

Severe asthmatics tend to have increased symptoms compared to mild asthmatics. If symptoms worsen, it is usually in the second and third trimesters, with the peak occurring in the sixth month. There is generally improvement in asthma during the last four weeks of pregnancy.

During labor and delivery, only 10% of asthmatics experience difficulty, which is usually mild and easily controlled. Asthma tends to return to the prepregnancy state by 3 mo

postpartum. Successive pregnancies tend to have a similar course in each individual.

Every asthmatic should be maintained on appropriate medications and followed carefully throughout pregnancy, especially in the second and third trimesters. Asthma specialists should be readily available for collaborative care when there is an exacerbation. Timely adjustment in treatment for any changes that might occur in asthma course will ensure the best control of the disease in the face of complex multiple influences.

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