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Asthma and Pregnancy

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Approximately 6 million women under the age of 45 are affected with asthma (1). It is estimated that 0.5-1.3% of all pregnancies are complicated by maternal asthma, making asthma one of the most common complications of pregnancy (2).

The Effects of Pregnancy on Asthma

Asthma symptoms vary in relation to the severity of the disease during pregnancy. Approximately 1/3 of asthmatic women report more severe symptoms during pregnancy than before. 1/3 report less symptoms, and 1/3 report their asthma symptoms remain unchanged during pregnancy. About 2/3 of all women report some dyspnea during pregnancy.

Asthmatics enter pregnancy with preexisting problems limiting breathing and lung function. In all pregnant women, changes in function and capacity of the lungs, and pressure on the chest wall are attributed to the circumferential expansion of the uterus. Consequently, during pregnancy asthmatic women need to be particularly aware of their ability to inhale adequate amounts of air (3).

Several theories have been postulated about the discrepancies between changes in asthmatic symptoms during pregnancy compared to preconception. There have been reports of individual women who experience improvement of symptoms with one pregnancy, and worsening of disease in their next. Becroft et al (4) suggested that the sex of the fetus might influence the course of asthma during pregnancy. In a blind prospective study, they found that 50% of mothers of females reported increased asthmatic symptoms during pregnancy compared to 22.2% of mothers of males. Furthermore, mothers of males tended to report an improvement in their asthmatic symptoms (44.4%), while none of the mothers of females indicated any improvement. These researchers postulate that the adrenergic surge experienced by a woman while carrying a male fetus might mitigate her asthma.

The Effects of Asthma on Pregnancy

Asthmatic women are at an increased risk for several complications during pregnancy. Adverse fetal outcomes associated with asthma include pre-term delivery, low birth weight, small size for gestational age and increased length of hospital stay. The pregnant woman with asthma is at risk for experiencing preeclampsia, placenta previa, caesarian delivery and increased length of hospital stay (2).

In pregnancy, the arterial blood gases are typically close to the following values: PO₂ remains near 100 mm Hg, arterial pH increases to 7.40 to 7.45, and arterial PCO₂ slightly decreases to 25 to 32 mm Hg. Hypoxia is the state when oxygenation of the arterial blood and tissues falls below normal. Status asthmaticus or severe asthmatic exacerbations can result in this dangerous state. A minimal change in

maternal blood oxygen concentration may result in appreciable changes in fetal oxygen content. Fetal oxygen requirements increase exponentially with gestational age. The exact level of hypoxia that causes fetal death is unknown. A maternal PO₂ <60 mm Hg portends fetal jeopardy. For these reasons, it is crucial for the asthmatic mother to realize that she is breathing for herself as well as her fetus (3). Relative maternal hypoxia has been shown to lower infant birth weight in otherwise normal pregnant women, e.g., women who live at a high altitude (5).

Pulmonary function can be quantified by FEV₁ (Forced Expiratory Volume during 1 second) and compared to a predictive value based on height and weight. Schatz et al (5) studied pulmonary function throughout pregnancy in 360 asthmatic women. They found a small, but statistically significant correlation between infant birth weight and average maternal FEV₁, measured monthly throughout pregnancy: the lower the mother's pulmonary function, the lower the weight of her baby. Even when these clinicians controlled for smoking during pregnancy, this correlation remained significant (5).

Controlling Asthma During Pregnancy

The results from studies on the safety of asthma medications during pregnancy have been conflicting. It is difficult to determine if adverse pregnancy outcome(s) in an asthmatic woman is a result of the disease, or other confounding factors. Most studies conclude that asthmatic medications are non-teratogenic (6,7,8). However, these conclusions are difficult to interpret because the study populations tend to be small.

Common Asthma Medications

Often asthma treatment involves the use of corticosteroid. In general, the use of corticosteroids (inhaled and/or oral) during pregnancy has been associated with an increased risk for cleft lip, with or without cleft palate. A population study, carried out in Spain, examined 1,184 infants and found that maternal use of corticosteroids correlated with a 6-fold increase in risk for cleft lip, with or without cleft palate. Although this figure appears to represent a large increase in risk, there were, in fact, only 2 cases of oral clefting associated with corticosteroid exposure, compared to the expected rate of 0.2 (8).

At Northwestern University, 80 pregnancies with first trimester exposure to oral and/or inhaled corticosteroids were evaluated and 2 infants were found to have congenital malformations. There were no infants in this series born with an oral cleft; the malformations included one infant with a ventricular septal wall defect and the other with Down syndrome. Since the general population risk for birth defects is between 3-5%, the 2.5% of infants with congenital malformations in this study was well within the expected range. This study concluded that use of corticosteroids during pregnancy did not increase this risk (9).

Most studies do not support a large teratogenic risk, however the association of corticosteroid use and clefting cannot be excluded. For more information regarding Corticosteroid Use in Pregnancy, please see RISK Newsletter Volume 8 No.1, April 2000.

Several reviews of current literature have assessed the safety of common asthma medications during pregnancy (10,11). These will be briefly reviewed in the remainder of this newsletter.

Inhaled Corticosteroids:

(beclomethasone, budesonide, fluticasone)

These are long-acting, prophylactic medications. Studies have demonstrated that continued use of inhaled corticosteroids throughout pregnancy does not increase the risk for birth defects or other pregnancy complications. Inhaled corticosteroids are considered the prophylactic medication of choice in pregnant women with persistent asthma, with beclomethasone being the preferred inhaled corticosteroid during pregnancy.

Oral Corticosteroids:

(prednisone, prednisolone)

Most studies assure non-teratogenicity of these medications, but there have been reports of an increased risk for oral clefting (see information above). Oral ingestion of medication increases maternal serum concentration of the corticosteroid above that of inhaled doses. One study found oral corticosteroid use associated with a slight increased occurrence (1-2%) of preeclampsia, preterm birth and low birth weight, with a dose-response relationship. This association was not replicated in groups using inhaled corticosteroids. However, the risk/benefit ratio warrants use of oral corticosteroids during pregnancy in patients with severe asthma (6). Derivatives of cortisone and prednisone are recommended since they are more readily inactivated by the placenta, as opposed to tamethosone or dexamethasone, which are not.

Short-Acting Beta Agonist:

(metapoterenol, terbutaline, albuterol)

Numerous studies found no adverse effect associated with using these medications during pregnancy. This medicine is usually inhaled, for fast-acting relief of asthmatic symptoms. Albuterol is the medication of choice in this category for use in pregnancy.

Salmeterol:

This medication is taken by some patients prophylactically to prevent an asthma attack. This newer long-acting prophylactic inhaler has very limited human research. Use of salmeterol is not recommended during pregnancy unless its therapeutic benefits cannot be matched by other medications.

Nebulized Ipratropium:

This medication is used for treatment of acute asthmatic symptoms. Animal studies suggest ipratropium can be considered for pregnant women who do not respond to inhaled beta agonist therapy, but there is no data on human exposure.

Neodocrimil:

No studies on the teratogenic effect of nedocromil are available. It is generally not as effective as inhaled corticosteroids and is not recommended for use in pregnancy over better-researched alternatives, unless a patient has responded well previously.

Leukotrine Modifiers:

This type of medication seems to be very effective in prophylactic management of mild to moderate asthma, but has not been compared to older medications. No human data exploring its use during pregnancy has been published. It is not recommended for use during pregnancy, unless it has shown increased therapeutic effects in a patient over better-known medications.

Theophylline:

This medication is used as a fast-acting bronchodilator. Some research indicates an associated risk for preterm birth, congenital malformations, and preeclampsia, while other studies have not found such associations. The effectiveness of theophylline, as compared to medications with established effectiveness, is questionable. Theophylline therapy is not recommended for use.

SUMMARY

In conclusion, aggressive treatment of maternal asthma during pregnancy is often appropriate. The goal of this treatment is to avoid asthma attacks throughout pregnancy. Since maintenance of a mother's health is crucial for optimal pregnancy outcome, good control of asthmatic symptoms, and avoidance of asthmatic emergencies is essential. Women with controlled asthma can expect to have the same pregnancy outcomes as non-asthmatic women (9).

References:

- (1) Middleton, Ed. (1998) Allergy: Principles and Practice, 5th Edition Mosby, Inc. St Louis.
- (2) Demissie K, Breckenridge MB, Rhoads GC (1998) Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 158:1091-1095.
- (3) Coleman MT, Rund DA (1997) Nonobstetric conditions causing hypoxia during pregnancy: asthma and epilepsy. *Am J Obst Gynecol* 177:1-7.
- (4) Beecroft N, Cochrane GM, Milburn, HJ (1998) Effect of sex of fetus on asthma during pregnancy: blind prospective study. *BMJ* 317:856-857.
- (5) Schatz M, Zeiger RS, Hoffman CP, and Kaiser-Permanente Asthma and Pregnancy Study Group (1990) Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. *Chest* 98:389-392.
- (6) Schatz M, Zeiger RS, Harden K, Hoffman CP, Chilingar L, Petitti D (1997) The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 100:301-306.
- (7) Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, Saunders B, Porreco R, Sperling W, Kagnoff M, Benenson AS (1995) Perinatal outcomes in the pregnancies of asthmatic women: a prospective analysis. *Am J Respir Crit Care Med* 151:1170-1174.
- (8) Rodriguez-Pinilla E, Martinez Frias ML (1998) Corticosteroids during pregnancy and oral clefts: a case-control study. *Teratology* 58:2-5.
- (9) Greenberger PA, Patterson R (1988) The outcome of pregnancy complicated by severe asthma. *Allergy Proc* 9:539-543.
- (10) Luskin AT (1999) An overview of the recommendations of the Working Group on Asthma and Pregnancy. *J Allergy Clin Immunol* 103:S350-S352.
- (11) Position Statement (2000) The use of newer asthma and allergy medications during pregnancy. *Annals Allergy Asthma Immunol* 84:475-480.