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ASTHMA AND PREGNANCY: WHEN YOU HAVE TO THINK OF TWO (OR MORE) INSTEAD OF ONE

BACKGROUND

Asthma is the most common chronic disease in pregnancy affecting 3 to 12% of women.[1] Poor asthma control is associated with adverse outcomes for both the mother and child.[1] Unfortunately, nearly half of asthmatics[2] discontinue or alter their asthma medication during pregnancy leading to diminished asthma control, and increased risks for mother and fetus from asthma exacerbation, manifesting most often in the middle-to-latter third of gestation. The triggers for asthma exacerbation are the same with or without pregnancy, mainly non-adherence to medications and viral infections. A significant association exists between severe asthma exacerbations in the first trimester and congenital malformations in the fetus as demonstrated in a 2015 publication in which the prevalence of any congenital malformation was 19.1%, 11.7% and 12.0% among women with severe, moderate and no such exacerbations during the first trimester, respectively. The adjusted OR for all malformations in this retrospective cohort study was 1.64 (95% CI 1.02 to 2.64) including cleft lip or palate, heart malformations and spina bifida when women with severe exacerbations were compared with those in the reference group, while no association was seen for moderate exacerbations. Asthma exacerbation can lead to maternal hypoxia which in turn affects fetal development and has been linked to congenital malformations.[3] Accordingly, appropriate treatment in this patient population is essential (**Table 1**).[4]

Pulmonary physiology during pregnancy

Functional residual capacity decreases significantly due to changes in chest wall compliance, but total lung capacity decreases only 5%. Best clinical practice suggests obtaining spirometry at each clinical visit as in non-pregnant women. FEV1 and forced vital capacity (FVC) are not affected by pregnancy leaving the FEV1/FVC ratio unchanged and so FEV1, FVC and the FEV1/FVC ratio remain reliable measurements to monitor asthma. Declines in spirometry reflect real changes in airway patency[5] and therefore in pregnant women with asthma any such decrease in spirometric measurement should be of concern. Hormonal influences on the respiratory center increase minute ventilation 30-50% due to increased tidal volume rather than respiratory rate.[6] Increased abdominal girth contributes to dyspnea in late pregnancy.

Fetal-maternal risks during asthma and pregnancy

Adverse outcomes may include preeclampsia, placental abruption, placenta previa and increased caesarian delivery.[7] In a cohort of asthmatic and non-asthmatic women linking [3] administrative data bases from Quebec, the

	Hospitalisation for asthma (n=110)	ED* visit and no hospitalisation for asthma (n=1413)	No hospitalisation and no ED* visit for asthma (n=35 064)
Any congenital malformation, n (%)	21 (19.1)	166 (11.7)	4196 (12.0)
Major congenitalmalformation, n (%)	13 (11.8)	107 (7.6)	2384 (6.8)

**ED, emergency department.*
Table 1. Prevalence of congenital malformations according to the level of asthma exacerbation in the first trimester of pregnancy: severe (hospitalization), moderate (ED visit and no hospitalization) and reference group (neither ED visit nor hospitalization).

prevalence of spontaneous abortions was 15.9%. Maternal asthma was associated with an increased risk of spontaneous abortion (OR= 1.41) and uncontrolled asthma increased the risk of spontaneous abortion by 26%.[8] Poor asthma control may even affect fertility.[9] Comorbid maternal conditions such as an increased risk of gestational diabetes may normalize with good asthma management.[10]

Poor asthma control can lead to numerous pediatric complications including low birth weight and small-for-gestational-age (SGA) infants. Uncontrolled asthma on two or more occasions during pregnancy may worsen perinatal outcomes even more so than exacerbations. Interestingly, female fetuses are at increased risk for SGA infants while male fetuses tend more towards preterm birth suggesting that fetuses may adjust to pregnancy stresses in a sex-specific manner. [11] Pregnant asthmatics have an increased risk of respiratory viral infections including the common cold[12] and influenza[13] and co-morbid conditions such as rhinitis[14] GERD[15] and sleep apnea may worsen during pregnancy.[16]

Management of Asthma in Pregnancy

Asthma management in pregnancy follows the usual general principles emphasizing symptom control, prevention of exacerbations and preservation of lung function. Discussion with the patient on therapeutics should emphasize the minimal risks and highlight the benefits of appropriate therapy and to develop an independent treatment plan with which the patient is comfortable. Monthly assessments are recommended by GINA (Global Initiative for Asthma).[17] A written asthma control plan should be developed for each patient.

Nonpharmacologic measures

Smoking cessation should be discussed prior to pregnancy. Data from the UK has demonstrated that the few documented tragic deaths in pregnant asthmatics have occurred in smokers.[18] Sensible allergen avoidance measures should be encouraged. Allergen immunotherapy (AIT), subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) should not be initiated during pregnancy due to the potential risk of anaphylaxis. Patients who have tolerated AIT and are maintained on their AIT with clinical benefits may continue their AIT.[19]

Pharmacological Therapy

INHALED AND ORAL CORTICOSTEROIDS (ICS AND OCS)

ICS are the mainstay of drug therapy in asthma. ICS suppress eosinophilic inflammation resulting in improved symptom control, fewer exacerbations and lower mortality. Pregnant patients, concerned about the potential teratogenic effects of any medication including ICS, will often stop inhalers but the deleterious effects of uncontrolled asthma for both mother and fetus are well documented.[20]

WHAT ARE THE FACTS ABOUT RISK VERSUS BENEFIT FOR ICS?

In a meta-analysis of aggregated data from three cohort studies of more than 500,000 pregnancies in Norway (2004-2010), Wales (2000-2010) and Funen, Denmark (2000-2010) a small increased risk of congenital anomalies for women taking asthma ICS medication was observed.[21] Studies based on medical registries in Denmark and Quebec looking at thousands of mother-child pairs showed that ICS treatment during pregnancy is not associated with fetal risk of congenital malformations particularly at doses of less than 1000 µg/d of beclomethasone. Corticosteroid -regulated pathways in the fetus are not affected by ICS use, reassuring the safety of ICS on fetal development. Doses greater than 1000 µg/d of ICS confirm a minimally increased risk of congenital malformation[22] but this requires cautious interpretation as the role of residual confounders such as uncontrolled or severe asthma have not been fully elucidated.

Budesonide (Class B) has long been considered the safest ICS during pregnancy. Recent data confirm fluticasone and beclomethasone are equally safe.[23] Newer ICS such as ciclesonide, mometasone and fluticasone furoate lack long-term safety data but are likely equally safe. A switch of ICS to budesonide during pregnancy is rarely warranted but may be preferred by some patients interested in ICS with the longest safety profile.[24]

The underuse of ICS increases the likelihood of asthma exacerbations thereby requiring the use of OCS. Prednisone is the most commonly-used OCS but about 90% of the blood concentration is inactivated by placental 11ß-HSD-2. Nevertheless, evidence suggests an increased risk of fetal cleft lip and palate with OCS use in the first trimester highlighting the need to maximize asthma control prior to conception. Overall, the benefits of OCS, when warranted clinically, outweigh the risks of sub-optimal asthma therapy.[25]

Bronchodilators

BETA-2-AGONISTS

Beta-2-agonists are known to inhibit airway contractility. Short-acting beta-2-agonists (SABA) such as salbutamol and terbutaline are safe in pregnancy. Long-acting beta-2-agonists (LABA) include the slower onset of action salmeterol, fast-

acting formoterol, and longer (24h) acting vilanterol and indacaterol. Salmeterol has the longest track record of clinical use and formoterol has not been associated with teratogenic effects. Both are safe for use in pregnancy[26] and should always be used in combination with an ICS. Once-a-day ICS-LABA combinations lack adequate safety data in pregnancy and should not be first-line therapy unless adherence is a significant issue.

SABA alone is no longer recommended by GINA. Canadian guidelines now recommend SABA alone only for very mild asthma at low risk for exacerbation.[27] SABA alone should not be used in pregnancy and should always be accompanied by a dose of ICS even for exercise induced symptoms. Budesonide-formoterol use p.r.n. is an alternative. Although not specifically studied in pregnancy, the individual components are safe, and the strategy has been confirmed in mild asthma.[28]

ANTIMUSCARINICS, LEUKOTRIENE MODIFIERS AND THEOPHYLLINES

Short-acting antimuscarinics (ipratropium) are sometimes used in asthma exacerbation and are considered safe in pregnancy.[29] Long-acting anti-muscarinic antagonists (LAMAs) are recommended as adjunctive therapy for more severe asthma that is not optimally controlled by combination therapy with an ICS-LABA combination.[17,27] Perinatal outcome data is lacking but usually LAMAs are continued during pregnancy.

Leukotriene modifiers are used mainly in mild asthma or as adjunctive therapy to ICS-LABA combinations.[17] Their clinical benefit is modest, and a leukotriene modifier should not, in general, replace an ICS in pregnancy. However leukotriene modifiers are generally considered to be safe in pregnancy[30] and so can be continued during pregnancy if effective and well tolerated prior to pregnancy.

Theophyllines are rarely used to treat asthma but are considered safe in pregnancy.

Biologics

Biologics are monoclonal antibodies (mAb) used to treat moderate to severe asthma, mediated by IgE and/or eosinophils. Biologic treatments are IgG-based and as a result they do cross the placenta,[31] but no evidence of teratogenicity has been observed to date.[32] Biologic agents can maximize asthma control in appropriate candidates prior to conception. Successful therapy with biologics prior to conception is usually continued but would rarely be instituted during pregnancy itself due to lack of specific data and the small risk of anaphylaxis.[32] Omalizumab is an anti-IgE mAb with two decades of clinical experience in patients with severe atopic asthma. Omalizumab significantly improves asthma control, prevents exacerbations and decreases the overall use of corticosteroids. A recent analysis of a cohort of pregnant asthmatics using omalizumab (EXPECT)[32] showed that proportions of major congenital anomalies, prematurity, low birth weight, and small size for gestational age observed in the EXPECT registry are consistent with findings from other studies in this asthma population and therefore do not suggest higher incidence from use in pregnancy.

Mepolizumab and reslizumab, biological agents that directly inhibit IL-5 (interleukin-5) and benralizumab which binds to the IL-5 receptor, have been successfully used in patients with severe eosinophilic asthma. Primate studies have not shown any adverse fetal effects.[34] Specific data in pregnancy and lactation is lacking, but no evidence of harm has been noted.

Dupilumab inhibits IL-4 and IL-13 by binding to the IL-4 receptor alpha and is indicated for severe asthma and with other Type 2 diseases such as nasal polyposis and atopic dermatitis. Clinical response is predicted by higher levels of FeNO and serum eosinophilia. Dupilumab use in pregnancy has limited data and should be reserved in pregnancy when other agents with registry data have failed or cannot be used.

Can biomarkers be useful in asthma management in pregnancy?

A FeNO-based algorithm to adjust ICS and LABA in pregnant asthmatics showed an important reduction in asthma exacerbations as well as improvements in quality of life and reduced neonatal hospitalizations.[35] ICS doses were increased earlier in eosinophilic

KEY CLINICAL TAKE AWAYS

Asthma is the most common chronic disease during pregnancy.

Asthma exacerbation is most common between weeks 24 and 36 of pregnancy.

Uncontrolled asthma before and during pregnancy is harmful to mother and fetus and good asthma control prevents complications such as pre-eclampsia, premature birth and small for gestational age infants.

Current asthma medications and in particular inhaled corticosteroids, bronchodilators and biologics are safe to use during pregnancy and promote asthma control.[33]

Asthma care for pregnancy should begin before conception.

asthma and, for asthmatics with low inflammatory markers, the doses of ICS were decreased and LABA introduced earlier leading to better asthma control. Further study of this interesting phenotypical approach to treat asthma in pregnancy is needed.

Considerations during labour

During labour, usual inhalers should be continued and induction therapy such as oxytocin and prostaglandin E2 are considered safe.[36] Prostaglandin F2 alpha derivatives should be avoided in cases of obstetric bleeding, if possible, as they can cause bronchoconstriction. Stress protocol hydrocortisone can be considered for the patient who is cortico-dependent or after an OCS boost prior to delivery.

Conclusions

Uncontrolled asthma in pregnancy is harmful to mother and fetus. The clinical benefit and innocuity of current asthma medications in pregnancy is well established. Most of the anti-inflammatory medications available for asthma whether alone or in combination with long-acting bronchodilators can be safely used in pregnancy and the choice should depend on factors such as ease of use and likelihood to promote adherence.

The establishment of a therapeutic relationship between patient and health care professional and regular follow-up during pregnancy is essential.[37] Asthma care for pregnancy should begin well before conception for any asthmatic considering having a child to ensure optimal asthma care, encourage discussion of the risk-benefit profile of different medications and to facilitate coordination of care with the obstetrics or family medicine team.

Algorithm for asthma management in the MAP (Managing Asthma in Pregnancy) trial*

	FeNO concentration (ppb)	Symptoms (ACQ score)	IS dose change	B2-agonist dose change
Level 1	>29	NA	ICS x 1 step	No change
Level 2	16-29	<1.5	No change	No change
Level 3	16-29	>1.5	No change	LABA x 1 step
Level 4	<16	< 1.5	ICS x1 step	No change
Level 5	<16	>1.5	ICS x1 step	LABA x 1 step

FeNO=fraction of exhaled nitric oxide. ACQ=asthma control questionnaire. ICS=-inhaled corticosteroid. NA=not part of the assessment at this FeNO level. LABA=longacting B2 agonist.

Table 2: Dose changes based on FeNO and ACQ results for the FeNO intervention algorithm

	ICS step	B2 step
Step 1	0	Salbutamol as required
Step 2	Budesonide 100 ug twice per day	Formoterol 6 ug twice per day
Step 3	Budesonide 200 ug twice per day	Formoterol 12 ug twice per day
Step 4	Budesonide 400 ug twice per day	Formoterol 2 x 12 ug twice per day
Step 5	Budesonide 800 ug twice per day	Formoterol 2 x 12 ug twice per day

FeNO=fraction of exhaled nitric oxide. IS=inhaled corticosteroid.

Table 3: FeNO algorithm treatment steps

The treatment algorithm used a two step process. First the level of ICS was adjusted using the FeNO concentration; then the ß2-agonist dose was adjusted using the Asthma Control Questionnaire (ACQ) score. A significant reduction in asthma exacerbations during pregnancy was demonstrated using this methodology. The mean daily dose of ICS was decreased and more LABA was used during the pregnancy.
**Powell et al Lancet 2011.*

Asthma Control Questionnaire[16] : a clinical tool to measure how well asthma is controlled

The total score is divided by 7. An ACQ score of < 0.75 denotes good asthma control; 0.75-1.50 denotes partial asthma control; >1.5 denotes poor asthma control; Juniper et al Eur Respir J 1999; 14: 902-7[38]

ASTHMA CONTROL QUESTIONNAIRE **Please answer questions 1-6** **Circle the number of the response that best describes how you have been during the past week**	
1. On average, during the past week, how often were you woken by your asthma during the night?	0 Never 1 Hardly Ever 2 A few minutes 3 Several times. 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning.	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3. In general, during the past week, how limited were you in your activities because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited"
4. In general, during the past week, how much shortness of breath did you experience because of you asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5. In general, during the past week, how much of the time did you wheeze?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time
6. On average, during the past week, how many puffs of short-acting bronchodilator (eg. Ventolin) have you used each day?	0 None 1 1-2 puffs most days 2 4 puffs most days 3 8 puffs is most days 4 9-12 puffs most days 5 13 -16 puffs most days 6 More than 16 puffs most days"
To be completed by a member of the clinic staff 7. FEV1pre-bronchodilator: ..... FEV1 predicted ..... FEV1 % precicted ..... (Record actual values on the dotted lines and score the FEV1 % predicted in the next column)	0 >95% predicted 1 95-90% 2 89-80% 3 79-70% 4 69-60% 5 59-50% 6 <50% predicted

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