WOMAN ASTHMATIC: BIOLOGICAL SEX DIFFERENCES AND GENDER IMPLICATIONS

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ABSTRACT

The impact of sex based biological differences on health and disease has been recently recognized, especially in chronic diseases including asthma. Increasing numbers of asthmatics worldwide makes it imperative to understand the disease process from different perspectives due to it's potential to impact individual's life and strain the resources available to the society. Epidemiological studies amongst asthmatic children show boys outnumber girls 2:1. After teenage years, data suggests not only women asthmatics outnumber men but may also have more severe asthma. The etiology of these differences is unclear as yet. The plausible explanations invoke differences amongst the two genders ranging from growth, TH1/TH2 immune processes, and hormonal differences during the childbearing age to socio-psychological response to disease process. Obviously the interaction of asthma and pregnancy is complex and can be detrimental for both if asthma is not well monitored and controlled. The response of the two genders to chronic diseases like asthma could differ due to differences in psychological makeup and the expectations by the society. There is a paucity of data on these issues. It is evident if the sex-based differences in asthmatics are true, the questions of different strategies in terms of therapeutic modalities, delivery of health care, economic and socio-psychological support need to be explored. This report presents an overview of sex and gender based differences in asthmatics.

INTRODUCTION

A growing body of evidence has highlighted the impact of sex based biological differences on health and disease. Concerns have been raised about lack of data on diseases in women. Frequently forgotten in the management of disease is the patient as a person who is part of a family and society. This sick person has obligations and roles, frequently gender based, which affect the way the health services are available to, and availed off, by the patient. Thus both sex and gender play an important role in diseases, especially chronic diseases including asthma.

Asthma in some estimates affects up to 32.1% of children, with boys out numbering girls in the age group less than 10 years by 2:1. In adults asthma affects 5-15% of population. Closer scrutiny of data suggests that adult women asthmatics not only out number men but also have more severe asthma. Asthma control has been recognized to be affected in some women during menstruation and pregnancy. This review on asthma in women is by no means exhaustive but is intended to present an overview of the problem, highlighting paucity of good studies in the hope that it will help focus attention and efforts to address the issues.

The current pathogenesis construct of asthma is based on TH1/TH2 immune processes. The CD4+ T helper lymphocytic response, based on profile of cytokine release, can be either TH1 (Interleukin-2, interferon γ) or TH2 (IL-4, IL-5, IL-10,IL-13). The type 1 lymphocyte response is to enhance the microbicidal capacity of the host defense against microbes and is characterized by inflammation leading to tissue destruction and damage. The TH2 cells via IL-10 along with IL-4 and IL-13 counteract the severe TH1 response besides participating in allergic reactions and elimination of helminthes. The activation or predominance of these immune processes is based upon genetic composition, exposure to environmental factors, including infections and other factors not properly understood. It is attractive to blame the recent increase in asthma prevalence and severity on the shift of balance in favor of TH2 response due to improvement of living standards, vaccination and antibiotics. In simplistic terms decreased childhood infections tilt the balance in favor of TH2 lymphocytes. The TH2 lymphocytes release cytokines (IL-4, IL-5, IL-13) that help recruit eosinophils and increase production of IgE antibodies by B-lymphocytes. The binding of antigen (allergen) with antibody (IgE) on the surface of mast cells and eosinophils triggers the release of mediators causing bronchospasm and airway inflammation. However, there are other factors
affecting the TH1/TH2 balance. Notably in pregnancy a predominance of TH2-cytokines, IL-4 has been reported\textsuperscript{21}; similarly there is an immune shift in favor of the TH2 response during the perimenstrual period\textsuperscript{22}. The evidence for effect of sex and gender on asthma and the implications of asthma for women will be reviewed.

**EPIDEMIOLOGY OF ASTHMA IN WOMEN**

The epidemiologic studies on asthma from 1940s-60s, regarded asthma largely as psychosomatic illness, predominantly focused on children and male adults\textsuperscript{23}. Following decades saw increasing participation/inclusion of minorities and women in studies. During this period epidemiological techniques were refined, the definition of asthma evolved from symptom-based diagnosis, demonstration of reversible airway obstruction, increased airway hyperresponsiveness to the presence of airway inflammation reflecting the increased understanding of its pathogenesis\textsuperscript{24-27}. Epidemiological studies of asthma are based on patient-reported asthma or wheezing, physician-reported asthma, and/or bronchial challenge tests of airway hyperresponsiveness\textsuperscript{8,13-16,28-33}. These methods appear to correlate with each other, but they make it very difficult to compare studies based on either one or varying combinations of criteria. The majority of the data shows a significant shift of asthma predominantly in males in the first decade of life\textsuperscript{8-10} to females in the next 4-5 decades\textsuperscript{13,16,34-35}. Some of the increase in reports of asthma in women no doubt is due to increased rate of diagnosis. However, recent well-designed studies examining the issue show a definite increase of asthma prevalence and confirm the reversal of sex ratios with age. The International Study of Asthma and Allergies in Childhood (ISAAC)\textsuperscript{8} found that the prevalence of wheeze in the previous 12 months in children aged 6-7 years ranged from 4.1-32.1% with boys predominating. The 463,801 children in the 13-14 year age group from 56 countries showed a greater prevalence in females along with a significant interaction with the country. Asthma prevalence from the second decade on decreases to reach adult levels. However, there is a definite increase of asthma in women there on as suggested by the data from Finland\textsuperscript{36}. This reversal in ratios seems to gradually reduce by the fifth to sixth decades of life, and data is scant in the elderly. The European Community Respiratory Health Survey (ECRHS) on 20-44 year old asthmatics from 48 centers reported female predominance from all centers except one. A retrospective analysis of this data for differences in incidence related to age in men and women consistently showed the risk for asthma in women after puberty higher than in men (relative risk ranging from 1.38-5.91)\textsuperscript{37} in all of the 16 countries studied. This data supports reports from U.S.A.\textsuperscript{15,16}, Finland\textsuperscript{36}, U.K.\textsuperscript{38,39}, Canada\textsuperscript{39}, Germany\textsuperscript{40}, Australia\textsuperscript{41}, Denmark\textsuperscript{42} and India\textsuperscript{13} suggesting similar epidemiological trends, although most of the studies were not designed to specifically address the question or have data which leaves itself open to epidemiological questioning. Perhaps more importantly under-diagnosis of asthma was observed in adolescents and was most prevalent in girls in the age group 12-15 years\textsuperscript{43}. Epidemiological reports unable to demonstrate these trends suffer from small study size, patient enrollment bias (generally for women), grouping teenagers with children, or simply because the study was not designed to address the issue\textsuperscript{43-49}. The issue of gender in asthma is frequently not addressed especially in countries in the east\textsuperscript{50}. Another confounding factor is that in some regions the questionnaires, even standardized ones (ISAAC) for epidemiological studies suffer from lack of conformity to the local language or widely accepted understanding of the words used. In general higher prevalence of asthma has been reported from English speaking countries\textsuperscript{5}. In some regions such as the Indian subcontinent young women frequently lack awareness or refuse to acknowledge symptoms due to societal pressures and taboos.

Interestingly two studies\textsuperscript{51,52} suggested that athletes competing at the top level reported a higher prevalence of asthma than the general population. In the 1996 U.S. Olympics team 15% (total study group: 699) of athletes had been diagnosed with asthma (compared to about 10% prevalence in the U.S.) and significantly more women reported asthma (19.5 vs. 14.3% in men p<0.05)\textsuperscript{51}. Nystad et al (2000)\textsuperscript{52} showed similar numbers for elite Norwegian athletes with odds ratio for women having asthma compared to men being 1.7. This increased prevalence of asthma in women athletes is in concordance with the increased prevalence of asthma in women.

The increased asthma in boys in the first decade of life has been blamed on shorter airways with smaller diameter as a proportion of lung parenchyma, compared to girls of same age (dysnapsis)\textsuperscript{53}. Thus minimal inflammation results in a significant change in airway resistance in boys, which disappears as they grow.
older. This may also be part of the explanation of reversal of sex ratios seen in epidemiological studies after puberty. Some researchers have also invoked the Yentl syndrome (under diagnosis and under treatment of diseases in girls from families with less education and lower socio-economic strata) to explain sex difference in prevalence of asthma in low-income families.

Data across countries indicates that the reversal of gender ratios around puberty persists through the reproductive years of women and it probably has some pathophysiologic explanation. It is likely these trends are a reflection of hormonal changes alone or in combination with other factors leading to increased severity of asthma in women. The gradual waning of female asthmatic preponderance to near equal levels in both sexes by the fifth decade of life suggest an important role for hormones. The obvious question is what does this mean for the individual asthmatic patient in the clinic?

SEX DIFFERENCES IN CLINICAL PRESENTATION OF ASTHMA

Questionnaire studies on the issue of gender and clinical presentation with asthma suggest a sudden change of odds ratio against females around age 12-13. Although symptoms associated with asthma exacerbation are similar, women more frequently report nocturnal cough than men. Recent controlled studies have demonstrated that women have a lower threshold for cough than men. Although, cough variant asthma was initially reported predominantly in women, on review it was found with equal frequency in both sexes. However, the issue of difference in clinical presentation of asthma in the two sexes has not been addressed in epidemiological studies on asthma. Increased severity of disease has been reported in women. Emergency room visits by asthmatic women are twice as numerous as those by men with asthma. Further higher incidence of hospitalization has been reported among female asthmatics than male asthmatics. Higher prevalence, increased severity, possibly better appreciation of symptoms, and more concern for their health may explain these numbers. Another factor explaining the increased use of health resources among adult asthmatic women could be a reluctance to use inhaled corticosteroid due to concern for side-effects. Over-reporting of morbidity by women with chronic diseases is not borne out by the few studies done in this area. The fear of osteoporosis is real but several studies have documented the role of steroid use in decreasing readmissions. Convery et al interestingly showed reduced efficacy of inhaled steroid fluticasone in women asthmatics compared to men asthmatics. This was a small study and the data begs for further studies.

MORTALITY DUE TO ASTHMA IN WOMEN

Data on the sex differences in mortality from asthma is also mixed. In Australia and UK where asthma prevalence is higher than other countries there is a tendency to higher mortality in women. This may be a reflection of more severe disease and/or under appreciation of severity of exacerbation. Estimates by the Centers for Disease Control, U.S.A. suggested age-adjusted death rate from asthma increased by 40% from 1982 to 1991 and the major burden of this increase was borne by women (59% vs. 34% in men). Further the prevalence of asthma in women increased by 82% compared to 29% in men during the same period. The CDC estimates, although not very reliable, suggest that in the U.S. more female deaths due to asthma than males (1993-95 data 20/100000 population vs. 15.1 in men). Same national estimates show higher number of female asthmatics with more frequent hospitalization, emergency room and doctor visits. At the same time, in the U.S, a study revealed asthma mortality is predominantly in Afro-American young males, perhaps due to socio-economic and other important social factors submerging other gender differences. Data signifies that besides gender other factors like race, socio-economical status also affect mortality due to asthma. Limited data from Russia also shows increased prevalence of asthma in women but the mortality due to asthma amongst women is higher than men above the age of 65 only.

MENSTRUATION-LINKED ASTHMA

Worsening and/or exacerbation of asthma in association with the menstrual cycle is reported by 25 to 74% of female asthmatics (Table 1). The worst period is the premenstrual week although the menstrual week
is also frequently problematic. Symptom scores correlate well with an objective fall in peak expiratory flow rates (PEFR) during this phase. A small minority of patients report worsening of asthma symptoms either in mid-cycle and/or during the menstrual week. Patients with menstruation-linked asthma have more emergency room visits and hospitalizations. A report of three patients with severe premenstrual exacerbation of asthma not responsive to high dose steroids yet relieved with progesterone therapy suggests a hormonal component to the disease. Interestingly Pauli et al (1989) in a controlled, prospective study with mild asthmatic women, unaware of menstrual association with asthma, recorded a fall in the morning PEFR and worsening of symptoms during the premenstrual week. Agarwal and Marshall (1999) published data suggesting healthy women have a perimenstrual shift in cytokine balance towards a TH2 response, which is blunted in women on oral contraceptive pills. Wjst and Dold plotted a graph of increasing asthma in children that was parallel to the use of oral contraceptive pill by women but this is probably a statistical association showing two true phenomena that are unrelated. To our knowledge there are only two case reports of worsening of asthma related to the use of the oral contraceptive pill. It is interesting to speculate that all this may be a reflection of psychological impact, fluid retention or autonomic lability due to premenstrual syndrome (PMS). A report linked menstruation with variation of skin reactivity to histamine. Although other allergies have been shown to be associated with premenstrual syndrome, a study from New Zealand did not find worsening of asthma to be associated with PMS. An interesting question to look at would be the impact of hormone replacement therapy in postmenopausal women asthmatics. Certainly the interaction of asthma with use of oral contraceptive pills is another area need to be investigated.

IMPACT OF PREGNANCY ON ASTHMA

Asthma prevalence in women in reproductive age group is around 10% and it reportedly complicates up to 4% of pregnancies. At the cellular level pregnancy seems to be more of a TH2 immune state, IL4 and IL5 having been associated with the course of pregnancy. The implications of fetal and placental production of the cytokines are not yet clear. Studies suggest equal proportion of asthmatics during pregnancy will improve, stay the same or worsen. Schatz et al (1988) reviewed 366 pregnancies. Asthma worsened during pregnancy in 35% of women, improved in 28% and was unchanged in rest. In patients with worsening of asthma the increase in symptoms occurred between 29 to 36 weeks of gestation. Worsening of asthma symptoms was seen during labor in 10% of women. About 18% of pregnant asthmatic women during pregnancy will visit emergency room once and over 2/3 of these will require hospitalization. In spite of repeated and forceful recommendations for the use of inhaled or oral corticosteroids for acute exacerbation of asthma during pregnancy, less than 2/3 patients are prescribed steroids by ER physicians. The majority of these patients will have ongoing problems even after two weeks thus potentially jeopardizing the outcome of pregnancy. This hesitation stems from the association of steroids with osteoporosis and fetal cleft palate.

Good asthma control before pregnancy and close monitoring through out is the ideal goal. As a rule severe asthmatics do poorly during pregnancy. The pattern of asthma during previous pregnancies predicts the course in subsequent pregnancies in over 2/3 of patients. Acute severe asthma seldom complicates labor. Post partum, over 3/4 of patients report asthma going back to baseline by about 3 months suggesting under appreciation of asthma symptomatology during pregnancy. Recent data in pregnant women with male fetus showed decreased requirement of steroids for asthma management. This observation needs further study.

Juniper and Newhouse (1993) in a retrospective analysis of 14 studies, found it very difficult to come to firm conclusions highlighting the need for well designed studies to investigate the interaction of pregnancy and asthma (Table 2). Pregnancy is also a standard exclusion criterion in the majority of studies upon which treatment efficacy and safety recommendations are ultimately based. Not surprisingly the evidence available for anti-asthma medicines does not meet the U.S. Federal Drug Agency level A evidence in support of their use during pregnancy.
IMPACT OF ASTHMA ON PREGNANCY

Mild to moderate asthma has no impact on pregnancy outcomes. Only patients with severe uncontrolled asthma have a worse outcome. This data is based upon women with universal access to health care, close monitoring and adequate control of asthma. Relationship between infant and maternal outcomes and asthma complicating pregnancy from historical cohort analysis after controlling for confounding variables demonstrated increased risk of adverse pregnancy outcome (Table 3). Women with an International Classification of Diseases, Ninth Revision diagnosis code for asthma (n=2289) were compared with 9156 randomly selected women from the remaining pool. Increased odds ratio for premature delivery, small for date baby, in utero death and in general poor outcome for fetus were observed. Further increased maternal risk for preeclampsia, caesarian section and longer hospital stay was also found. In these patients the placento-fetal unit is more susceptible to mild drop in arterial oxygen, while normal carbon dioxide levels on arterial blood gas analysis is a harbinger of risk to the fetus. Compounding the problem, pregnant women during asthma exacerbation are less likely to be prescribed corticosteroids, the drug of choice. Thus there is an urgent need for increasing physician awareness about adequate asthma control in pregnant women. Equally important is to target the women, emphasizing better pregnancy outcome with well-controlled asthma. There is small body of evidence suggesting association between allergen sensitization in babies with maternal smoking or maternal exposure to allergen during pregnancy. These associations need more intensive investigation.

ENVIRONMENT, ASTHMA AND WOMEN

Increasing asthma occurrence, especially in developed countries, has led to several studies on the impact of indoor environment. In the U.S.A. estimates suggest most people spend 90-95% of their time indoors. In the past this figure was much lower. Frequently the rooms have air-conditioning and carpeting. This provides an ideal milieu for house dust mites to thrive. Further ventilation rates as low as 0.3 air exchanges/hr help in stagnation of cigarette smoke, nitrogen dioxide from appliances, sulfur dioxide and formaldehyde from paints; and hair-dander from pets especially cats. Poorly maintained houses with old dust laden carpets, mould growing on walls and cockroach infestation contribute to morbidity. These may also reflect the socio-economic status of the patient, an issue that is also important. In the developing world women are exposed most especially to indoor allergens on cleaning and dusting the house. No data is available on the most common occupation - being a mother. Almost all mothers actively participate in looking after children, especially when they are sick or have a cold. Cooking and cleaning the house translates to greater exposure to the commonly incriminated allergens, and hence higher probability of sensitization. Women involved in cooking are exposed to various inhalants, at concentrations much higher than present in atmosphere of environmentally unfriendly cities. We know that smoking is associated with airway hyperresponsiveness, but housewives cooking on wood, cow dung and/or kerosene stoves have been studied only in a superficial manner. Limited studies show association of chronic cough and bronchitis with these exposures. In our experience several women complained about exacerbation of asthma on exposure to spices while cooking, an area not yet investigated at all. Lastly there is paucity of good data on impact of sex and gender issues on occupational asthma in women. A case control study from Goteborg, Sweden observed increased risk of asthma among males after exposure to flour dust, welding fumes, man-made mineral fibers and solvents. In females exposure to paper and textile dust were associated with increased risk for asthma. A case series of 55 occupational asthma patients, followed up after removal from the cause, were evaluated for the severity of asthma. Multivariate analysis showed odds ratio for increased risk of severe of asthma in women to be 13.8 (95% confidence interval = 1.3 - 151.7). Another analysis of data from 12 industrialized countries concluded that prevalence of occupational asthma in women and in specific occupations is underestimated. This data raises the need for good prospective well-designed studies to address the issue.
SEX AND ASTHMA

In a paper presented from The Harlem Lung Center New York\textsuperscript{111}, 66\% of 353 asthmatics reported asthma-related sexual limitation. Exercise induced asthma is another problem which interferes with quality of life. Energy consumption during intercourse is equivalent to climbing two flights of stairs\textsuperscript{112}. This could be a significant problem in poorly controlled asthma in either sex. Sircar and Shah\textsuperscript{113} reported coitus-induced asthma in patients who did not exhibit exercise asthma. Three out of four patients in the report were women. Interestingly a handful of cases of semen plasma allergy have been documented\textsuperscript{114-116}. During intercourse semen allergy could result in local allergic reaction or a systemic response like asthma. Condom use can help prevent contact with semen. Difficulty in getting pregnant and the psychosocial consequences for the woman in particular could cause distress.

ECONOMIC IMPLICATIONS OF ASTHMA FOR WOMEN

Asthma is no doubt an economic strain on the individual and the society. Asthma in the early sixties was considered a psychosomatic disease of upper-middle class children who were unable to take the strain of life. Now it has become a disease of inner city children frequently exposed to house dust mite and living in houses infested with cockroaches, a disease associated with lower socio-economic strata of the society\textsuperscript{23}. This group of patients has reduced access to health care facilities and frequently is unable to afford quality medical care. Countries like Sweden\textsuperscript{117} and U.K.\textsuperscript{118} with universal health coverage have successfully shown a decrease in inpatient admissions by control of risk factors, patient education and outpatient access for all. Even if there is only change of direct costs from in hospital to ambulatory care, the indirect benefit in terms of number of workdays saved (average hospitalization/attack in U.S. being 3.8 days and somewhat longer and more frequent for women), the impact on the ability of women to look after children and family is potentially large. Analysis of a database of 27 hospitals in U.S.\textsuperscript{119} revealed the cost per admission for asthma of 1074 patients over a period of one year was \$3102.53 while another 2,149 patients visited the emergency room costing \$234.48. A national estimate for the U.S. in 1994\textsuperscript{120} of direct costs due to asthma was 5.1 billion dollars. More than 80\% of resources were used by 20\% of asthmatics, an annual estimate per person of \$2584 compared to \$140 for the rest. A retrospective cohort analysis of 12,203 asthma patients showed a 3.5 times increased direct cost per asthma attack per patient vs. those who did not have asthma exacerbation. There was reportedly no difference in terms of cost with respect to sex. However, especially economically vulnerable were single mothers either with asthma, or those with children having asthma. In the U.S. 84\% of children stay with their single mothers\textsuperscript{121}. Similar concerns about the economic impact of asthma and financial benefits of improving primary care for asthma in ambulatory setting have been voiced from Switzerland\textsuperscript{122}.

SOCIO-PSYCHOLOGICAL IMPACT OF ASTHMA AND WOMEN

Asthma exacerbation during psychological stress in both sexes is well known. Psychological and psychosocial factors are associated with fatal and near fatal attacks of asthma. Lack of psychosocial support, psychiatric problems, personality disorders, social and employment stress have all been associated with "brittle" asthma, near fatal and fatal asthma\textsuperscript{123, 124}. Most of the data available is for children\textsuperscript{125, 126}, very few studies have specifically addressed the issues in adults and even less in women. Women interact with asthma not only as patients but also as relatives of asthmatic patients. Mothers tend to be more involved in care of asthmatic children, voice more concerns in terms of time, energy and tense atmosphere and have a strong tendency towards depression. Mother's emotional and psychological well-being has a tremendous positive influence not only on the asthmatic child but also on psychosocial adjustment of non-ill siblings. The impact of chronic illness on the sibling is yet an unexplored area. A strong impact on adaptation to stress is associated with support of family, friends, relatives, coworkers and neighbors. Importantly the marital satisfaction of the spouses of children with chronic disease also comes under threat\textsuperscript{127-130}.
Chronic diseases in the woman or child have been associated with increased divorced rate although in a small study this was not found in the case of asthma\textsuperscript{131}. Marital prospects among asthmatics especially in the developing world, is another area under explored. We have treated several women asthmatics who have never revealed their asthma to their spouses. These problems could easily be overcome by education of society, better control of asthma morbidity and tackling psychosocial issues.

Although there are several studies highlighting the significance of psychosocial factors in the control of asthma, data on women asthmatics and disease impact on the family are almost nonexistent. In a limited study of 50 couples, male asthmatics were found to have higher distress levels and less utilization of physician services\textsuperscript{132}. An analysis of predictors of physical functioning found none affecting the male patients. In female asthmatics psychological distress accounted for about 19\% of variance in their physical functioning while psychological symptom severity of their partner accounted for another 16\% of variance. Woman asthmatics got less psychological support from their spouses. Spouses' inability to handle stress especially of asthma was found; this may be even more marked in the developing world with additional contributions by poverty and lack of education. Not surprisingly more women turn to out of family support. Further in a market already in favor of men in terms of occupation and salary the impact of asthma on professional prospects of women needs to be studied.

CONCLUSIONS

Asthmatics face not only the disease, but also the social issues associated with the disease\textsuperscript{133}. The lack of data has resulted in inadequate knowledge about sex and gender issues in asthma. These issues assume a special, often painful, significance for women asthmatics. The problem is further compounded by lack of or limited availability of sex and gender sensitive access to and delivery of care. Through ignorance or oversight, the failure to use existing tools has lead to under-recognition of these issues. In developing countries the problem is especially acute. The lacunae in knowledge are:

1. Disease process:
   a) sex based differences in epidemiological trends
   b) sex based difference in clinical presentation and management
   c) asthma and its association with menstruation and pregnancy
   d) interaction of oral contraceptive pills, hormone replacement therapy and asthma
   e) occupational asthma in women

2. Psychosocial issues:
   a) psychological impact in terms of response to disease
   b) psychological impact on women in different roles - mother, spouse or child of an asthmatic
   c) acceptance of disease by family, coworkers and society
   d) strengthening of social networks for support

3. Economic issues:
   a) Direct financial impact on asthmatics especially in women
   b) Financial impact on family
   c) Financial, social support and impact on society and government

These are issues, which have enormous impact on morbidity due to asthma. How we handle the industrialization process and the environmental changes in Africa, India and China are questions to be considered. Women there are not only looking after home and family but also frequently working in underpaid, environmentally unfriendly surroundings, all with an impact on asthma. This is where the World Health Organization has a significant role to play.

ROLE OF WHO

The World Health Organization and National Institutes of Health have already organized - a "Global Initiative of Asthma" and declared May 3 as the "World Asthma Day"\textsuperscript{134}. Patient, physician and population
education are to be the main objectives. Asthma currently suffers from lack of large data sets, which could more completely answer many of the questions about gender issues. The majority of data is from retrospective analysis of asthmatics. Under the auspices of WHO large multi-centric trials and research, especially in the developing world, will help fill in the gaps of our knowledge about sex and gender issues in asthma:

1. Well-designed epidemiological studies to identify the impact of sex in asthma especially in the developing world.
2. Both basic science and epidemiological studies to help understand the association of asthma with pregnancy and menstruation.
3. Educate physicians about adequate control of asthma in women, especially during pregnancy
4. Formulate studies for reliable evidence investigating the safety of anti-asthma medications during pregnancy
5. Generate data and design studies for exploring the sex differences in response to steroids and other drugs.
6. Organize or help with financial support in terms of drugs
7. Set up a network of psychological support to women
8. Organize studies to investigate the stress of women asthmatic on family interaction and well being
9. Strengthen education programs for the population especially in the developing world with emphasis on schools and work places.

In conclusion, asthma seems to be more frequent in women throughout the reproductive years. This association is probably a reflection of hormonal changes and results in more severe asthma. Pregnant asthmatics need closer monitoring to avoid morbidity and improve fetal outcome. The economic burden of asthma in the current social scenario adds to women's problems, and psychological and emotional support required to accept a chronic disease is frequently lacking. Thus the added burden of asthma in asthmatic women is not only due to differences in biology and physiology, but also that of gender biases in terms of social, economic and psychological factors.

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94. Dodds L, Armson BA, Alexander S. Use of asthma drugs is less among women pregnant with boys rather than girls. BMJ 1999;318:1011.


121. Data from US Census internet site and Equal Employment Opportunity Commission Task Force on Equal Pay
Table 1: Studies investigating occurrence of menstruation-linked asthma (MLA)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
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<td>20 (74)</td>
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<td>Shames et al</td>
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Q - Questionnaire, D- Symptom Dairy, P - Peak expiratory flow, I - Interview, N - number of patients. Ref 73-77

Table 2: Studies investigating the course of asthma during pregnancy

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<tr>
<td>Sims et al</td>
<td>1976</td>
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<td>Gluck &amp; Gluck</td>
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<td>Schatz et al</td>
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<td>Stenius-Arniala</td>
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<td>White et al</td>
<td>1989</td>
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<td>Juniper et al</td>
<td>1989</td>
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</table>

N - number of female asthmatics studied. Adapted from Reference 95
Table 3: Impact of asthma on pregnancy (outcomes in odds ratio)

<table>
<thead>
<tr>
<th>Infant outcomes</th>
<th>Pre/Post term</th>
<th>1.36/1.18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth weight</td>
<td>1.29-1.32</td>
<td></td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>1.26-1.36</td>
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</tr>
<tr>
<td>Congenital anomaly</td>
<td>1.34-1.38</td>
<td></td>
</tr>
<tr>
<td>Hospital stay &gt;3 days</td>
<td>1.44</td>
<td></td>
</tr>
<tr>
<td>Maternal outcomes</td>
<td>Preterm labor</td>
<td>1.51</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.94-2.18</td>
<td></td>
</tr>
<tr>
<td>Placenta previa</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td>Hospital stay &gt;3 days</td>
<td>1.86</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Reference 97