Women and Wheezing: Differences in asthma in women and men

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Clinical case

- 52 yo, previously healthy, elite athlete. Relatively sudden menopause age 48. Within mos of menopause, severe respiratory problems, including 2 long intubations for asthma. Treated with high dose systemic steroids, xolair and typical care. Hospitalized almost monthly. Severe mucus plugging. FeNO 120. FEV1 from 28-55% predicted. No eosinophils noted.
- What would you do?

Hormonal therapy

- Various steroid approaches taken, none with any help
- Eventually begun on estrogen 0.625 mg
- Within 1 mo, remarkably better
  - No additional systemic steroids
  - FEV1 into 70-80% range
  - No ER/hospitalizations
  - FeNO still high (80-90)
- Maintained for >1 yr

Women and wheezing

- Many diseases more common/severe in women (ie, Lupus, Rheumatoid arthritis), including asthma
  - More adult women with asthma than men
  - Pregnancy, menopause, menstruation all impact asthma
- Males and females have "different" types of asthma
- Giving hormones to mice worsens asthma like symptoms
- Hormone supplements influence asthma

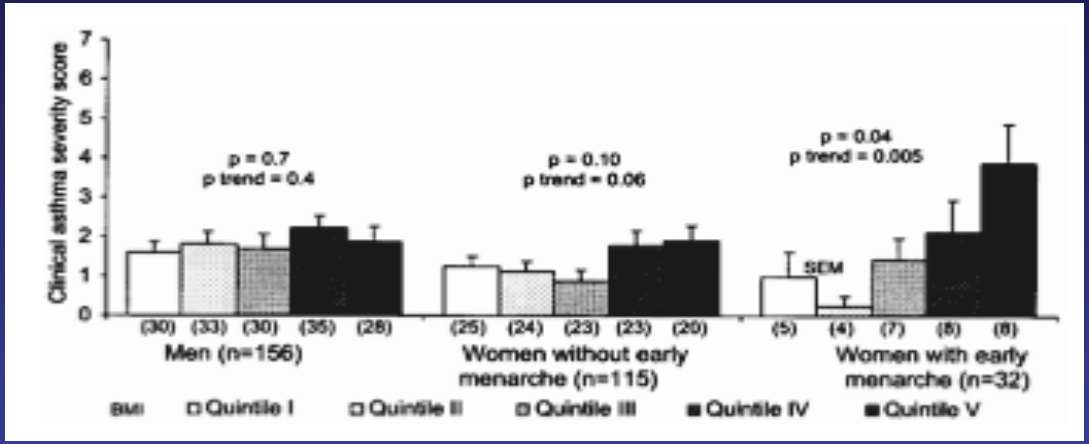
Asthma frequency in girls/boys as compared to women/men

- Childhood asthma more common in boys
- By adolescence, asthma more common in women, and incidence may increase with severity
- In ~1/3 of women, asthma related to hormone levels
  - 1/3 of women have worsening asthma during pregnancy, 1/3 get better!!
  - 1/3 of women have asthma worsening at time of periods

Increasing prevalence of asthma in women

- At adolescence, girls have greater likelihood of new onset asthma, while many boys "grow out" of asthma
  - Girls are more specifically allergic
  - Girls more susceptible to obesity which may also impact asthma
  - Earlier age of menarche associated with asthma severity and obesity Varasso AJRCCM 2005

Menarche and asthma severity

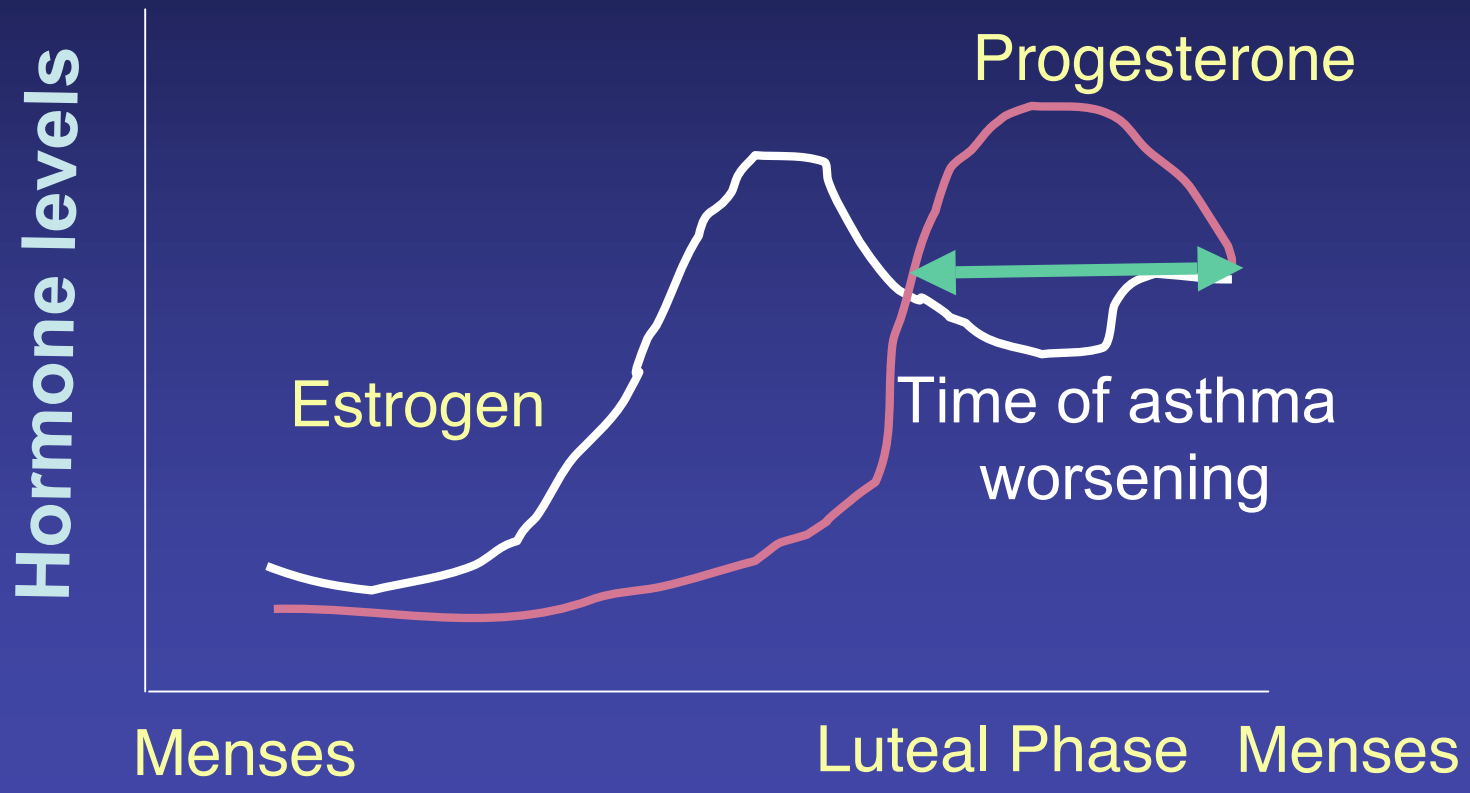


- Adolescence associated with increase in asthma in girls
- Early menarche related to obesity and associated hormone increases
- Combination of current obesity and early menarche associated with the most severe (adult) asthma in women (and men)

Perimenstrual asthma

- Up to 1/3 of women report worsening of asthma at time of menstruation
- Two separate studies suggest hormone levels during "luteal phase" before onset of periods associated with increased risk of asthma exacerbation
  - Skobeloff Arch Int Med 1996, Martinez-Moragon JACI 2004

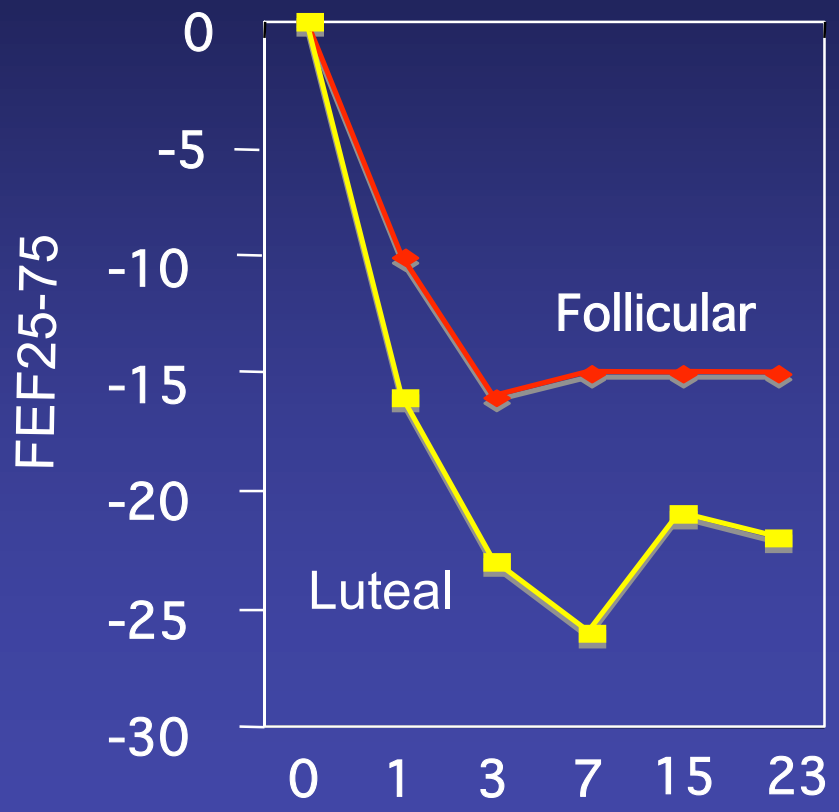
Hormonal cycle



Cyclic hormonal influences on EIB

- 7 female recreational athletes with mild asthma evaluated with exercise challenge during mid follicular and mid luteal phases
- Estrogen and progesterone levels obtained

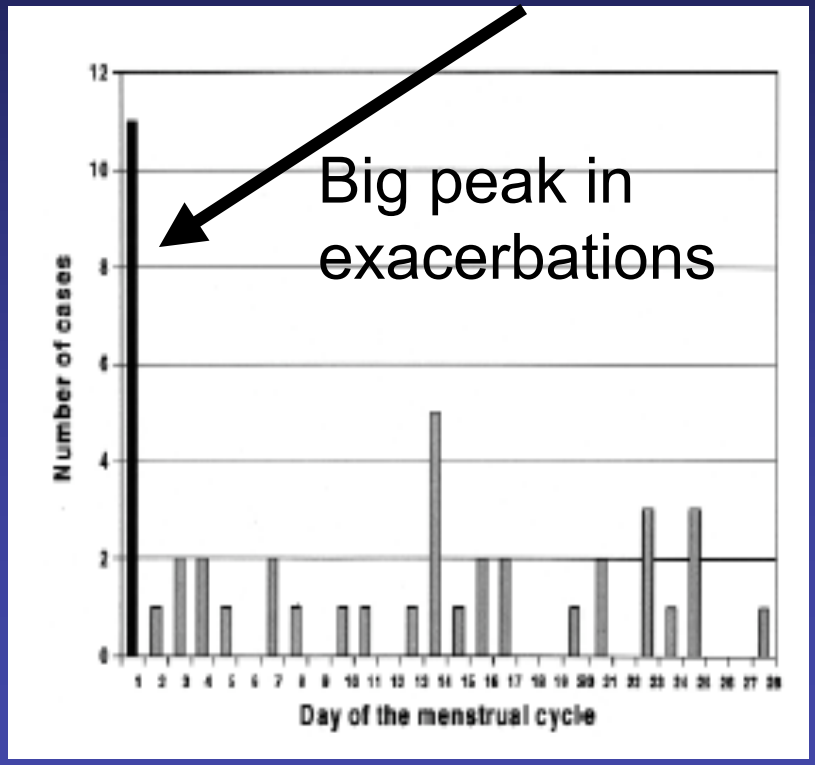
EIB and hormonal levels



- Significantly greater fall in FEF25-75 during luteal phase when progeseterone levels high
- Modest correlation with fall in FEF25-75 and change in progesterone levels

Stanford Eur J App Phys 2006

Perimenstrual asthma and near fatal events



- 44 women with history of severe asthma
- Most severe exacerbations of asthma occurred on day 1 of cycle following 7 day increase in symptoms
- Women with perimenstrual NFA more severe

Severe Asthma Research Program

- 8 sites in US and UK
- Specifically recruiting severe asthmatics with milder controls
- Over 500 subjects evaluated by questionnaire, eosinophils/IgE, PFTs, allergy tests
- Risk factors for severe asthma exacerbations identified

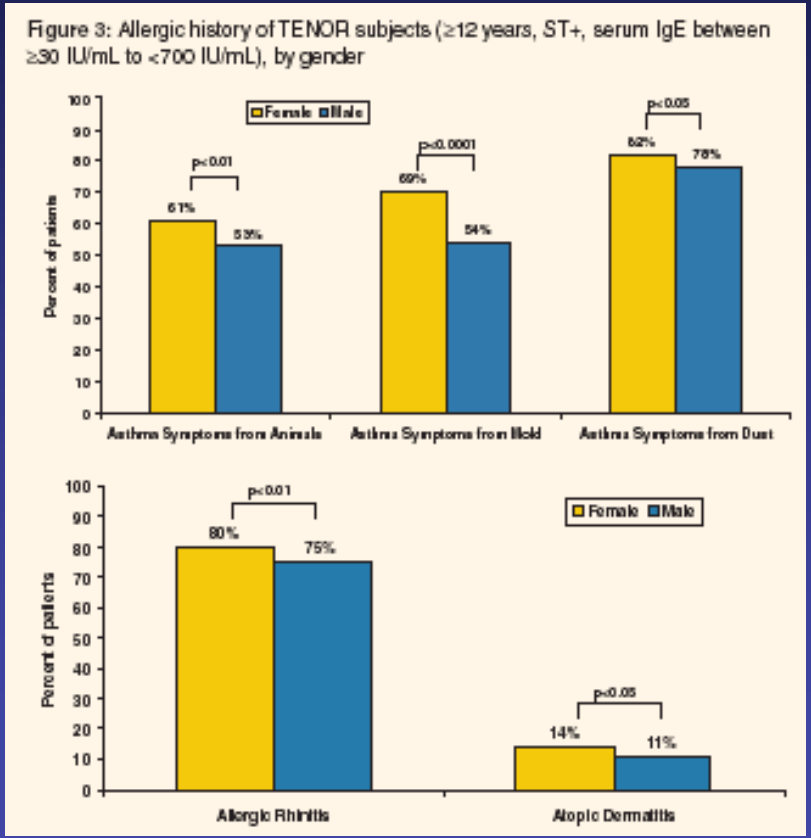
Risk Factors for very severe asthma

Risk factor	Odds Ratio	Confidence Interval	P-value
African American	3.00	1.68-5.36	=0.0002
Lower post-BD FEV1*	1.16	1.07-1.25	=0.0002
Age at onset†	0.96	0.93-0.98	=0.001
NSAIDs	3.59	1.69-7.63	=0.001
Peri-menstrual asthma	3.01	1.15-8.58	=0.02

Differences in male/female asthma

- Women have more specific allergic skin reactions and allergic symptoms
- Generally, women have more symptomatic disease, but, interestingly, less obstruction in their lungs than men do

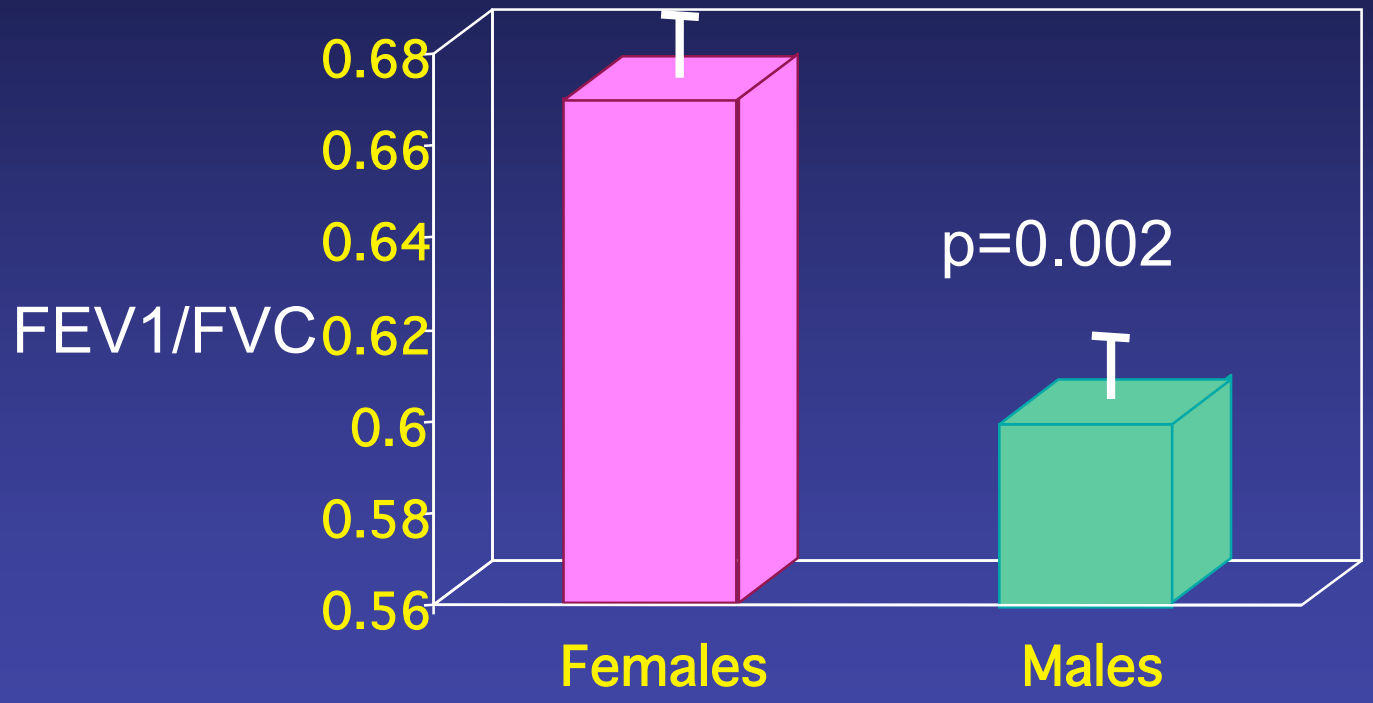
Asthma differences in men and women



- Women have greater allergic disease and more severe symptoms than men

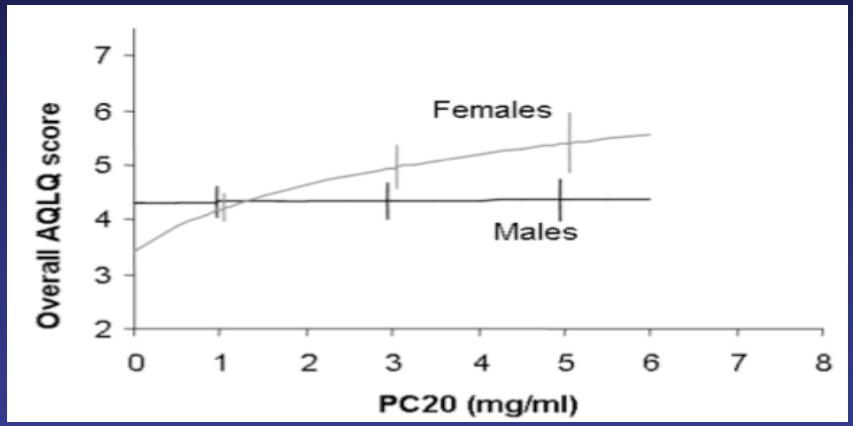
  Wenzel J Asthma 2006

Male asthmatics significantly lower FEV1/FVC than females



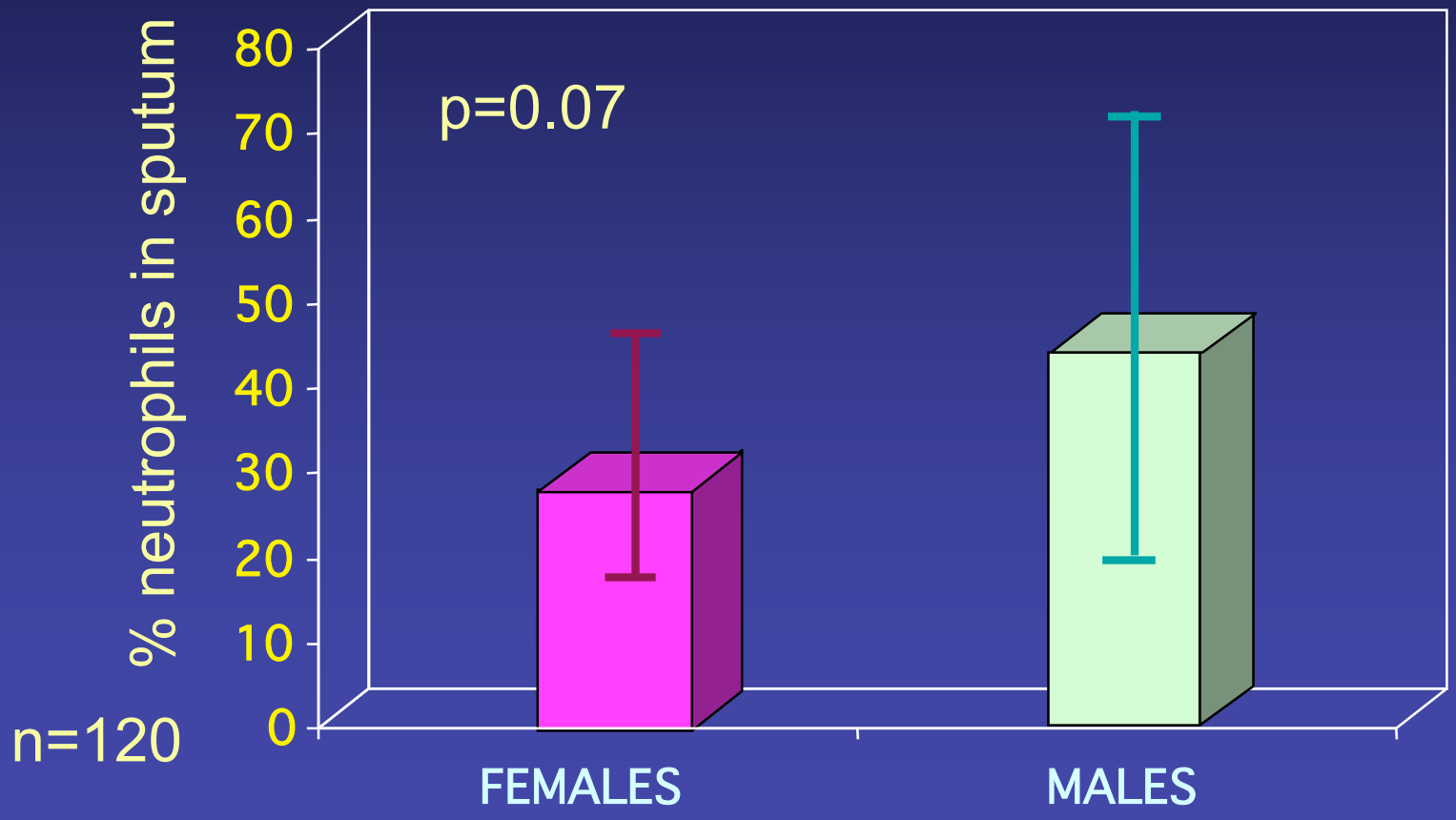
FEV1% predicted not significantly different, but ratio marginally lower in *normal* males vs females (84% vs 81%)
In contrast to obstruction, females may have lower PC20

Women may also respond differently to worsening PC20



- Study of AQLQ in mild to severe asthma
- The effect of PC20 on overall AQLQ is greater in women than men (women affected by worsening PC20 to greater degree than men
  - Busacker, submitted

Could differences in inflammatory pattern explain physiology?

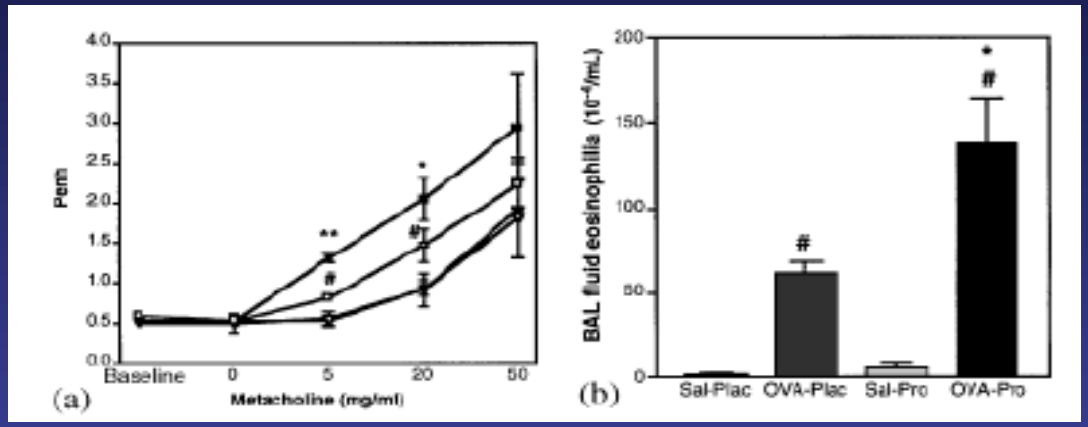


Neutrophils traditionally associated with lower FEV1

Animal models of asthma

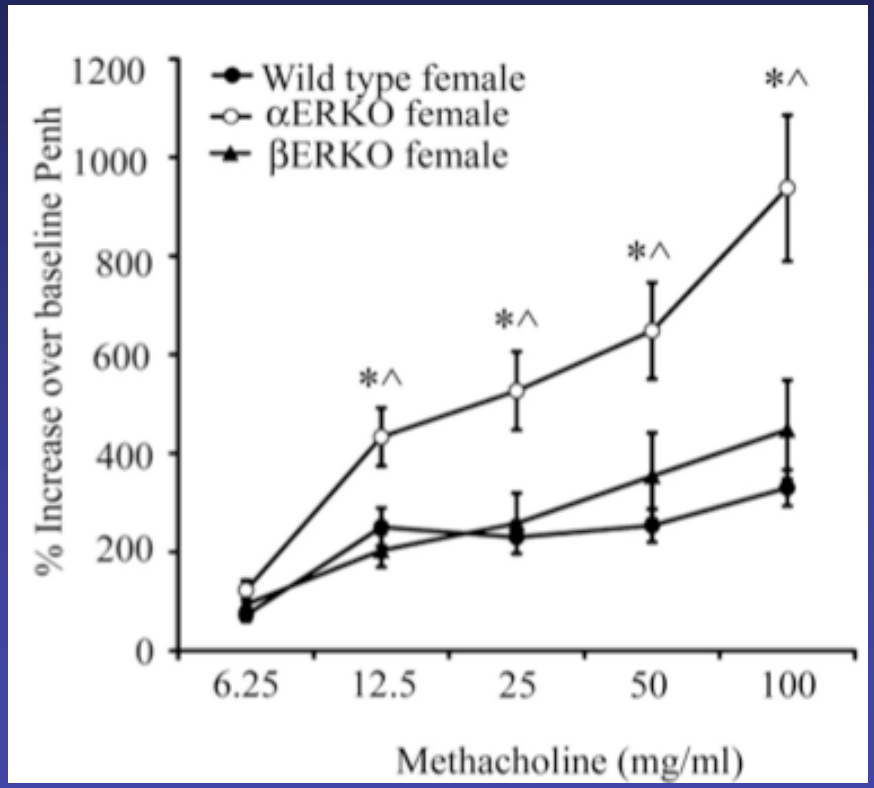
- Studies have suggested that giving hormones to male or female mice influences asthma-like responses
- Giving progesterone to male mice increased asthma reactions and lung inflammation in an OVA model Hellings CEA 2003

Progesterone and allergic inflammation



- Treating male mice with progesterone before allergic exposure increased airway twitchiness and inflammation
- Female mice with ovaries removed had *less severe* reactions

In contrast estrogen appears to be protective in mice



- Estrogen receptor alpha (-/-) mice, without any challenge, more reactive than WT mice Carey In press AJRCCM
  - No effect in ERß (-/-)
  - No effect of additional ovariectomy
    - **Suggests effect NOT due to progesterone**
  - Associated with loss of M2 receptors

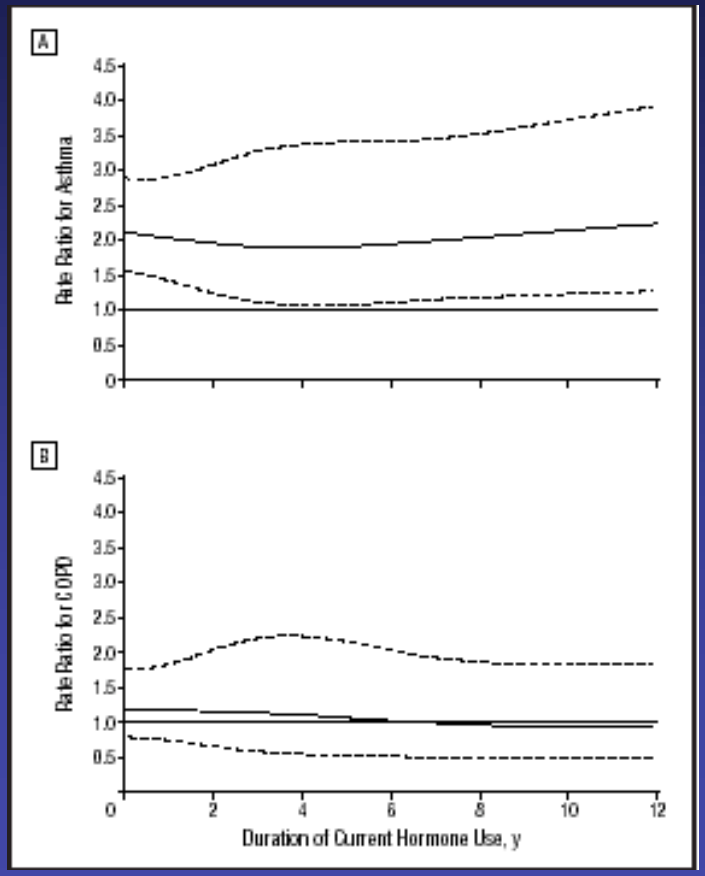
What about hormone replacement in women?

- Hormone replacement therapy (HRT) associated with greater risk for development of asthma in post-menopausal women (and younger women) without a history of asthma
- HOWEVER, in women WITH asthma, HRT markedly decreased wheezing

Nurses health study

- Over 120,000 women entered into study in 1976 Barr Arch Int Med 2004
- Hormone replacement therapy (HRT) use determined by questionnaire
- Asthma diagnosis based on physician diagnosis and questionnaire data over years of follow-up

HRT increases risk for asthma



- Risk for new onset asthma (in those without asthma) increases with duration of use of HRT (OR >2.0)
- Applies to both estrogen and combination Rx
- No impact on new onset COPD

Pre-menopausal women

- Children's Health Study evaluated respiratory health in over 6000 children in So. California Salam JACI 2006
- Follow-up study of nearly 1000 girls over 7 years
  - Age of onset of menstruation
  - Birth control pill use
  - Wheezing symptoms
  - Height, weight and age

Birth control pills and asthma

- In women without history of asthma, BCPs increased the risk for asthma symptoms by 60%
  - Mechanisms unknown
- In women WITH a history of asthma, BCPs decreased the likelihood of asthma-related wheezing by over 80%
  - BCPs suppress progesterone surge and may decrease asthma symptoms in this way

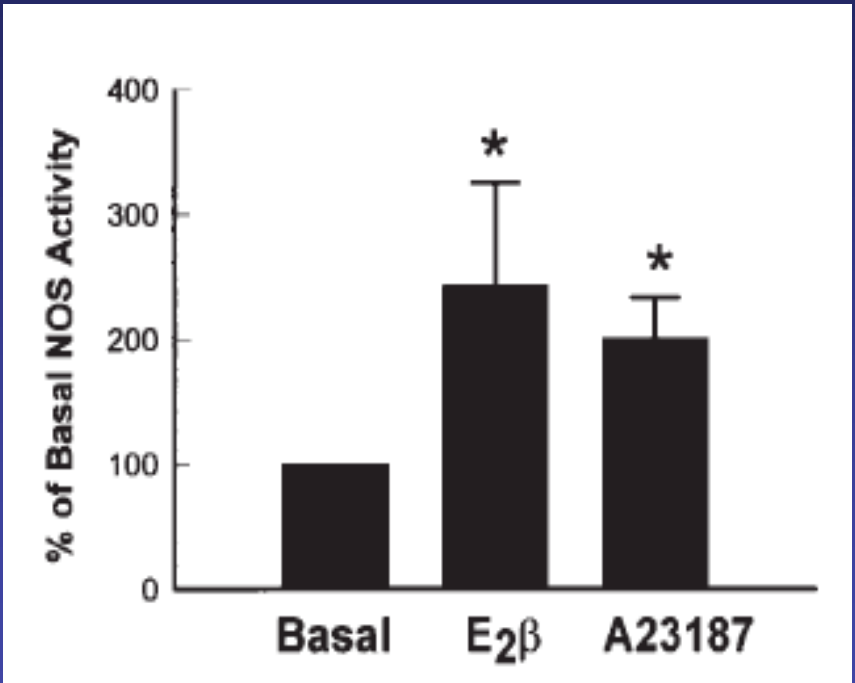
Few studies on hormones and asthma beyond symptoms

- Study of 11 women with asthma worsening with periods
- Significant increases in lung eosinophils and FeNO before menstruation
- Associated with increase in symptoms and airflow limitation
  Oguzulgen J Asthma 2002

Potential mechanisms

- How and why estrogens and progesterones increase asthma onset in women without asthma
  - HRT may improve asthma in women WITH asthma
  - IN both cases, mechanism not clear
- Estrogens and progesterones known to have effect on smooth muscle in uterus…what about the lungs?
- Almost complete absence of studies of hormones on lung tissue

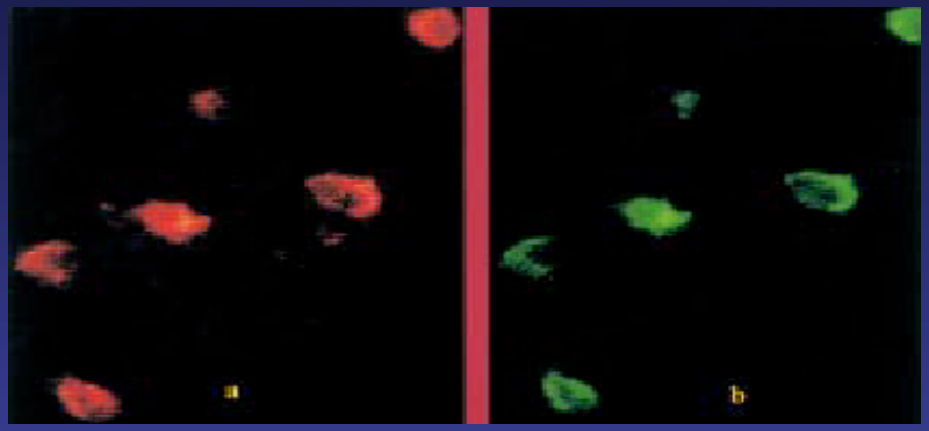
Hormones and lung epithelial cells



- Estrogen can interact with lung cells to increase inflammation, at least as measured by NOS activity
  Kirsch AJRCMB 1999
- But, MUCH more work is needed!

Possible effects on mast cells?

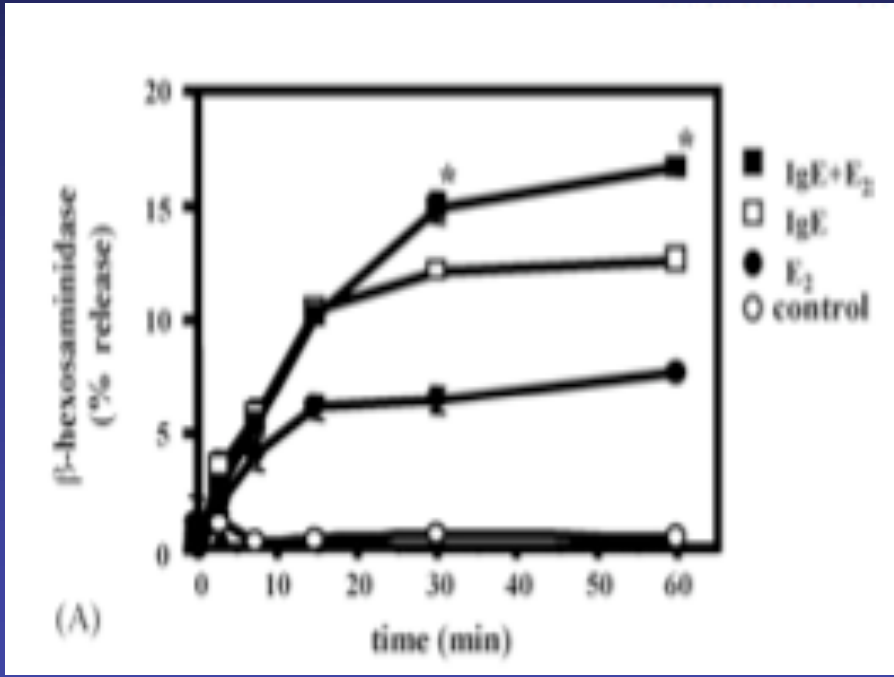
Mast cells



Progesterone receptor

- Mast cells known to be key cell in allergy and asthma
- Mast cells have both progesterone and estrogen receptors in lung tissue Zhao Thorax 2001

Functionality of receptors



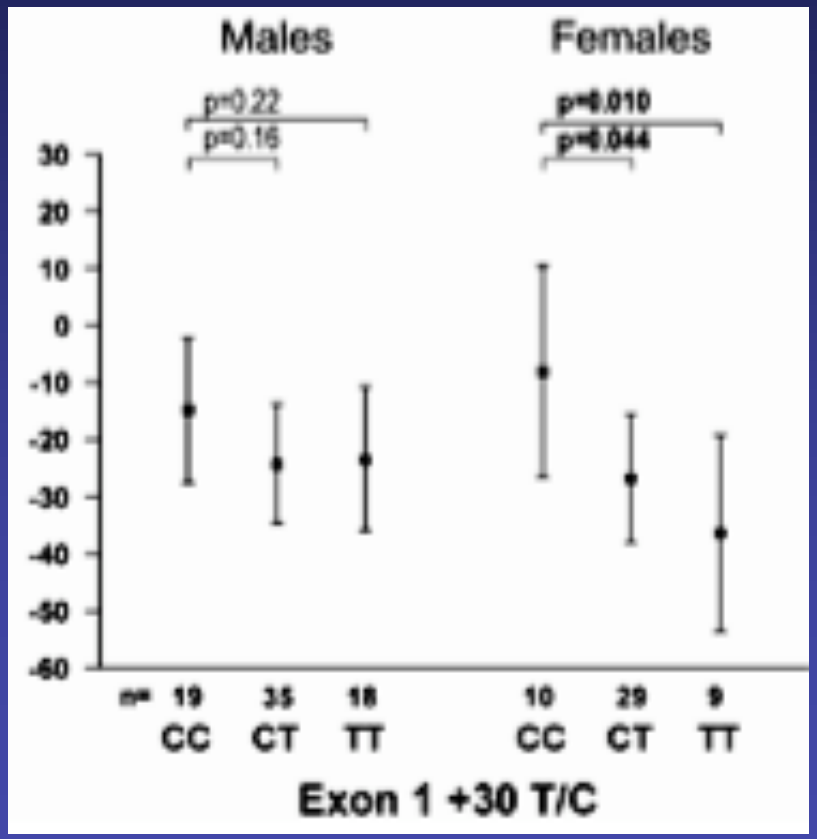
- Mast cell lines and bone marrow derived mast cells degranulate to estrogen
- Enhance effect of IgE on degranulation Zaitsu Mol Immunol 2006
- No studies have evaluated estrogen and progesterone in combination

Genetics of asthma and hormones

- Asthma IS hereditary disease
- Distribution of symptoms in relation to hormone issues suggests genetic influence
- Very recent study suggests that genetics of the estrogen receptor may influence asthma severity, esp in women (but also to some degree in men!)

Estrogen receptor genetics

Lung function



- Women with specific genetic variants appear to have more rapid decline in lung function
- Implies genetic alteration in hormone pathways influences lungs and their function

Conclusions

- Multiple studies suggest female hormones play big role in asthma
  - However, almost nothing has been studied as to why this happens
- BCPs CAN be tried as therapy for asthma in women with severe disease
  - However, women without asthma *might* do better without hormonal therapy
- Studies to explore the mechanisms behind these hormonal effects (and how to deal with them!) are urgently needed