Reviewer's report

Title: Effects of sex hormones on bronchial reactivity during the menstrual cycle

Version: 3 Date: 28 September 2013

Reviewer: Maarten van den Berge

Reviewer's report:

The authors have investigated the effect of the menstrual cycle and sex hormone levels on bronchial reactivity (BR) in a Group of PMA women. The main findings are that BR is increased in the follicular phase of the menstrual cycle in women and associated with lower cAMP levels in sputum samples which may contribute to bronchoconstriction. I have the following comments:

Major comments:

1. Background, page 4/5. The authors aimed to investigate the effects of the menstrual cycle in a group of PMA women. To this end, 36 asthmatic women were included. Importantly, a lot of information on the clinical characteristics of these patients is missing.
   A. - Did the subjects really have asthma? This is important, because many patients seem to have a PC20 methacholine > 8 mg/ml or even 25 mg/ml.
   - Did they use inhaled corticosteroids/LAMAs/LABAs?
   - I would suggest to include a table with the baseline characteristics and outcome of the measurements during the follicular and luteal phases.
   B.
   - Perimenstrual worsening of asthma has been reported in 30-40% patients. Importantly, the subjects included in the present study are referred as ‘PMA patients’, at least in the methods section. However, were they really all PMA patients? This appears not to be the case, since they did not have a perimenstrual increase in symptoms or BHR. This should be made more clear throughout the manuscript as it is currently confusing.
   C.
   With respect to the study design: When exactly were the measurements performed during the menstrual cycle, i.e. PFTs, PC20, blood collection? At day 1 of menstruation and 14 +/- 1 days after? Obviously this is crucial information which is currently lacking.

2. The authors did not find any difference in the severity of BR between the luteal and follicular phase. Nevertheless, they argue that 72% of patients had a lower PC20 FEV in the follicular compared to the luteal phase. Was there a difference when analyzing the data in this way? Although I do not feel the data to be very
convincing, I would describe these results in results section and then make a clearer decision in the discussion as to whether or not the severity of BR should be considered to be more severe the follicular phase.

3. The discussion with respect to testosterone is too long.

Minor comments:
1. PMA is described as an exacerbation of symptoms. I would suggest to change exacerbation to worsening in this context throughout the ms.
2. Methods. Study population. This section includes results which should be described in the results section.
3. Measurements of IgE mediated hypersensitivity. Very lengthy description and I am not sure why this is relevant.
4. An IgE level > 100 was considered as high probability of allergy. Do the authors mean total IgE? In that case, I do not agree as patients with non-allergic asthma often also have increased total IgE levels.
5. FEV1 or FEV1.0?
6. The direction of the associations is often very confusing.
   Example 1, page 14. “Our study documented a significant inverse correlation between BR and serum testosterone levels:"
   - First, according to figure 1, I think the authors mean a positive correlation rather than inverse correlation.
   - Second, does an increase in BR refer to an increase in the PC20 value or a more severe BR, i.e. lower PC20 value?.
   Example 2, page 15 “Although sputum levels correlated indirectly with sputum PDE levels”:
   What does this mean? A higher sputum testosterone is associated with lower sputum PDE? Please describe the results more clearly throughout the ms.
7. Results. Page 7. Start with the alinea describing the allergic profile? Why is this information important?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.