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Answering reviewers

REVIEW 1: (may 18, 2015)

The author reviews the topic of premenstrual asthma. Specific figures, tables and summary points comparing the studies and the limited evidence should be presented. For example figure related to the pathogenesis with the involved pathways and how they may overlap. The tables should not only present the different points but also the level of evidence that is available e.g. for treatment with reference to specific studies and their limitations. Overall the data can be better presented and synthesized.

The tables have been modified substantially, as well as incorporating a higher level of evidence. Given the difficulty in establishing PMA pathogenesis we have not included any figure relating to that issue.

REVIEW 2: (may 18, 2015)

Pereira-Vega and Sánchez-Ramos have written the review manuscript about questions relating to premenstrual asthma. There are several spell (spelling) mistake and grammar errors should be improvement (be improved). However, the manuscript is good enough to (for) publication.

The grammatical errors have been corrected.

REVIEW 3: (may 30, 2015)

General comment;

This review article correctively sheds light on a variety of the issues concerning premenstrual asthma (PMA), which have not been conclusively settled. The reviewer is quite convinced that it is extremely important to make an effort to answer the unsolved questions in PMA from a clinical and pathophysiological point of view. As such, the reviewer considers that this article is potentially valuable for the readers in the field of pulmonary medicine.

However, there are some parts in the text, for which the reviewer feels difficulty to grasp (has difficulty in grasping) their essential meanings. This is due to the

erroneous English. Therefore, the reviewer absolutely requires the authors to let the manuscript checked by an English-native scientist again.

Furthermore, there are the terms in which the definitions were not clear (see below). These unclear terms should be changed to those with appropriate definitions.

The manuscript has been revised again by a native English speaker, with special focus on the grammar.

Major comments:

1) P. 4, "All this seems to indicate ..."; this sentence may be erroneous in grammar.

According to the translator who revised the text, this expression is correct in English.

2) P.4, "...question the very existence of "subjective" PMA by querying whether this exacerbation of symptoms ..."; what is meant by this sentence?

This section has been rephrased, with what we hope is a clearer explanation of the subjective PMA concept.

3) P. 5, "...a reduction in lung volume and flow, or diffusion ..."; what is meant by diffusion? The diffusion is not the same as the lung diffusing capacity for carbon monoxide (DLco). In the lung-function tests, we measure the DLco, in which a couple of phenomena regulating the gas transfer in the lung are involved; i.e., the ventilation-perfusion mismatches, the diffusive processes in the gas phase as well as the alveolar membrane, and so on. The term of "diffusion" indicates the pure physical phenomenon that is impossible to be measured in a clinical setting.

"Diffusion" has been substituted by "lung diffusing capacity"

4) P.5, "...non-peak flow parameters"; It is necessary to concretely define the lung-function contents given by the non-peak-flow parameters.

This has been reworded: "parameters different from peak flow". This refers to a citation of Pauli et al., in which no deterioration was found in spirometry or in bronchial reactivity (objective parameters that differ from peak flow)

5) P. 5, the last paragraph, "...semi-objective PMA ..."; the term of semi-objective PMA was not clearly defined in the text. This is (an) important issue so the authors should define the details of this term.

This section has been amended, with what we hope is a clearer explanation of the semi-objective PMA concept.

6) Related to the issue as described above (P.5), based on their own investigation, the authors stated "we consider the semi-objective criteria in a

complete menstrual cycle as the most valid approximation to real PMA". However, they did not present the reason why the semi-objective criteria acted as the most valid approximation to the PMA. This is the important and useful point for the readers to judge the clinical significance of each criterion when diagnosing the PMA.

We have clarified the reasons why we selected semi-objective deterioration in a single cycle:

1. We found that the biggest differences between the preovulatory and premenstrual phases in asthmatic females occurred within the semi-objective PMA category.
2. There is a greater correlation between the semi-objective exacerbation of the symptoms and perception of the exacerbation of the asthma before menstruation when considering one single menstrual cycle than requiring semi-objective exacerbation in two consecutive cycles.
3. Objective criteria, which demand a peak flow variation of 20%, are much more restrictive

7) P. 6, 16 lines from the bottom (2.2.- Questions on the relation between premenstrual asthma and premenstrual syndrome), it is not understood the reason why the authors inserted the word of "Edema" there.

Corrected. It now reads: edematous symptoms.

8) P. 7, " ...environmental factors could influence the development of PMA ..."; the authors did not explain the environmental factors related to the PMA in a concrete manner. This is one of the interesting points while considering the etiological substances eliciting the PMA. Therefore, the authors should make it clear what are the environmental factors related to the occurrence of the PMA.

In reality, rather than "environmental factors", a more suitable expression would be "other factors" such as sensibility to aspirin (ASS)错误!未定义书签。 , use of aspirin or non-steroidal anti-inflammatory drugs" ...

9) In Table 1, the authors depicted many possible factors related to the PMA. However, this table may not be useful from a clinical point of view. This is due to the fact that, from this table, it is impossible to discriminate between the factors related to the general asthma and those specific to the PMA.

The authors should provide a tactful (?) table or figure that makes (it easier for) the readers to easily understand the factors unique to the PMA, including genetic, biological, and environmental factors that have been demonstrated so far.

The reviewer suggests the authors make a figure in which the interconnection between a variety of the intrinsic and environmental factors forming the pathological aspects of the general asthma and those possibly specific to the PMA.

Table 1 has been redesigned completely; it now refers exclusively to PMA etiology. Given the difficulty in establishing PMA pathogenesis we have not included any figure relating to that issue.

Name: Antonio Pereira-Vega



Signature:

Date: 14/08/2015

Name: José Luis Sánchez-Ramos



Signature:

Date: Date: 14/08/2015