Author’s response to reviews

Title: Subcutaneous implant with etonogestrel (Implanon(R)) for catamenial exacerbations in a patient with cystic fibrosis: a case report

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Author’s response to reviews: see over
30th of September, 2014

Dr. Catherine M. Greene  
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Dear Editor:

Enclosed please find the revised version of the manuscript (case report) **MS 3701439591265411**. “Subcutaneous implant with etonogestrel (ImplanonR) for catamenial exacerbations in a patient with cystic fibrosis: a case report”. Authors: Adelaida Lamas AL, Luis Máiž LM, Marta Ruiz de Valbuena M R-V, José Manuel González-Casbas and Lucrecia Suárez

We appreciate the reviewers’ comments and insightful suggestions on how to improve our submission. Below please find our response to their helpful comments (in bold).

**Comments from Reviewer #1: Dr. Sanjay Chotirmall**

**Major Comments**

1. Abstract: I think the conclusion needs to be re-worded to “The potential of treatment directed at hormonal manipulation such as that with oral contraceptives or subcutaneous implants should be considered in suitable cases”: **We really appreciate this suggestion and have changed the sentence in the article by paraphrasing your words.**

2. The graph summarizing the patients clinical course and treatment is excellent but I would suggest if the authors are agreeable the use of colour coding for ease of identifying patterns for the reader: **Thank you for your kind words. We agree with your assessment and we have introduced colour in the graph.**
3. As the patients genotype was not your usual expected, could the class of mutation play a role in hormonal responsive CF disease? The authors should discuss this in the discussion portion of the manuscript.

As suggested, we have now included the paragraph below (in italics) in the discussion (line 185).

The genotype of this patient (R334W, class IV mutation, and Q890X, class I mutation) is uncommon and, in this case, associated with a severe expression of the disease with pancreatic sufficiency, numerous episodes of acute pancreatitis, and severe pulmonary disease with frequent PE. Sutton et al [16] analyzed the United States CF Foundation Patient Registry for a retrospective study of LF decline and rate of PE changes in CF before and after puberty. They concluded that whereas males had lower rate of PE than females, there was no association between annual frequency of PE and race, pancreatic insufficiency, or genotype. Further research is necessary to shed light on the relationship between CF genotype and the effect of female hormones on morbidity/mortality in women.

4. I think the discussion (particularly in the early portion) is rather confusing to read and needs again to be re-written by a native English speaker in order to clearly communicate to the reader the points (which are valuable) that the authors are attempting to make.

As per your suggestion, the entire manuscript has now been reviewed and edited by a native English-speaker medical writer. We hope the results are satisfactory.

5. The authors should hypothesize in the discussion the roles of estrogen versus progesterone in CF and additionally the differences between endogenous and exogenous estrogen? – This should be an additional new paragraph in the revised manuscript.

Thank you for the suggestion. We have rewritten de Discussion to elaborate on the roles played by estrogen vs. progesterone and endogenous vs. exogenous estrogen on women with CF. Additionally, we have added a new paragraph (below in italics) pulling that discussion all together (starts in line 195):
The effect of female hormones on women with CF is a complex issue given that women have different PE recurrence patterns according to the different phases of the menstrual cycle. Thus, studying the history of PE pattern is essential in order to prescribe one contraceptive method over another (with exogenous E, P, or a combination of both) according to the expression of clinical symptoms of each patient.

Minor Comments

We thank the reviewer for taking the time to bring these misspellings to our attention.
1. Subcutaneous catheter should be re-worded as “port-a-cath.” See line 99.
2. Spelling ‘hypophysis.’ See line 159.
4. Spelling ‘pattern’: Different locations

Comments from Reviewer # 2: Dr. Catherine Greene

Major Compulsory Revisions
1. Was the Pseudomonas that was isolated prior to and once after the insertion of Implanon mucoid or non-mucoid?
Non-mucoid Pseudomonas aeruginosa was isolated four months after the insertion of Implanon®.

2. Were serum estradiol levels ever measured in this individual? If so please include the data.
No, estradiol levels were never measured in this patient. We now include that information in line 130.

3. It is surprising that the exacerbations occurred exclusively in the luteal phase. Can you confirm this? Were there any exacerbations during the follicular (and in particular the proliferative) phase of the cycle when estradiol levels are also high?
We agree that it is surprising. Still, we are able to confirm that all the pulmonary exacerbations followed the same pattern, they always occurred four days before the menstrual period, during the luteal phase.

Minor essential revisions

4. In figure 1, please insert the right hand arrow head on the oral azithromycin indicator.

Thank you, it has now been inserted as suggested.

5. Please revise the text for correct spelling and English language editing throughout e.g. change hypofhysis to hypophysis, lutheal to luteal, endogen to endogenous, studding to studying, patron to pattern etc.

Thank you for pointing these errors out to us. They have all been corrected (see our response to Minor Comments from Reviewer #1).

Thank you again for these comments. Please do not hesitate to contact me with any further questions, comments, and/or suggestions. We hope these revisions satisfy the reviewers’ comments and we look forward to hearing from you.

Best Regards,

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