Author’s response to reviews

Title: Are pelvic adhesions associated the pain, physical, emotional and functional characteristics of women presenting with chronic pelvic pain? A cluster analysis

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We thank the reviewer for their constructive comments. Our response to the reviewers comments is as below:

Andrea Rapkin (Reviewer 1): The manuscript presents the results of hierarchical cluster analysis of demographic and clinical characteristics and adhesion scores for 62 women undergoing laparoscopy for chronic pelvic pain. The authors found that the reported pain and other characteristics have little or no correlation with adhesion scores and that most women who had adhesions had low pain scores.

1) In the Background, first paragraph, the author's state that there are currently no effective interventions for chronic pelvic pain and cite references 5 and 6; reference 6 was withdrawn and shouldn't be included in the bibliography. Reference 5 is a meta-analysis of single treatments which obscures the fact there are publications supporting multidisciplinary management. One in particularly germane to the current study is Peters AA et al 1991 describing a RCT of an integrated compared to traditional medical and/or surgical management.

Response: We have now removed the withdrawn reference. We have also included the comment made by the referee with regards to the relevance of multidisciplinary care (page 3, lines 88-89).
2) In the second paragraph the author's state that they have shown that "adhesiolysis may only benefit a subgroup of patients, and cite references 5 and 7. Reference 5 is a review of non-surgical management. Reference 7 is of interest; however the study was stopped before recruitment reached the statistically powered sample size due to low enrollment, so results are questionable. In addition, studies which do not show improvement in pain were omitted, e.g. Swank DJ Lancet 2003.

Response: We thank the reviewer for the comments. We have now removed reference 5. The two relevant references should be Peters AA, 1992 and Cheong YC 2014. We have added the point on premature termination of the study of Cheong YC 2014. We have referenced the negative study (Swank et al) to provide a more balance narrative (page 3 lines 92-95).

3) In the second paragraph the authors state there is some evidence to suggest dense vascular adhesions are more likely to result in pain, and that adhesions attached to ovaries are more likely to result in pain, two references are cited, 6 which was withdrawn and therefore should not be cited, and 8, Peters et al. However, a study by Rapkin in 1986, did not find an association between density or site of adhesions and pelvic pain. A retrospective study by Steege and Stout (1991) found the presence of psychosocial compromise was associated with a lack of salutary response with adhesiolysis. The findings are relevant to this attempt to develop a phenotype associated with adhesions

Response: We thank the reviewer once again for providing these insightful comments and references. We have included these suggestions on page 3, lines 99-102.

4) Authors should describe the meaning of clinical phenotype in this setting, and cite publications whereby clinical phenotypes can be helpful for guiding management in patients with chronic pain. Not all readers are familiar with the concept of phenotype unrelated to genotype.

Response: We thank the reviewer for suggesting this point. We have added this explanation in our introduction Page 4 lines 164-165.

5) In the Methodology section: Patients were excluded if they had psychiatric disorders for which they were taking medication. Please justify why such patients were excluded. Were all patients receiving some form of medication for chronic pelvic pain excluded, or just those receiving hormonal medications i.e., anticonvulsants or tricyclic antidepressants? Were subjects assessed for co-morbidities outcome such as presence of comorbid chronic pain or psychiatric diagnosis or history of physical, sexual or psychological trauma? If not why were such factors excluded and how does this impact the outcome, given that co morbidities and trauma impact chronic pain?

Response: We apologies for not making this clear. We have now clarified that psychiatric illnesses excluded included diagnosed mental disorders such as schizophrenia, bipolar disorders, psychosis etc. We felt that on several levels, in terms of consent, and the severity of their mental
illnesses, we would not be able to compare them to the general group of patients included in this study.

6) For the patients in the study who came to the point of undergoing laparoscopy, were other common causes of other chronic pelvic pain queried or excluded, i.e., abdominogl wall and pelvic floor myofascial pain, neuropathic pain, irritable bowel syndrome, and bladder pain syndrome? These need not have been exclusionary, but other comorbid pelvic pain disorders would affect the outcome of the current study and therefore the methodology should be further detailed. If not ruled out, how does this affect the outcome of the current study?

Response: We did not specifically exclude these disorders (abdominal wall and pelvic floor myofascial pain, neuropathic pain, irritable bowel syndrome, and bladder pain syndrome) and have stated this point in our discussion. Our study only focussed on the presence and absence of adhesions, and it is quite possible that if we were to tease the above-mentioned conditions out, the results may well be different. However, the diagnosis of abdominal wall and pelvic floor myofascial pain, neuropathic pain, irritable bowel syndrome, and bladder pain syndrome is not routinely carried out by the vast majority of practitioners in this context, and hence such data is not available to us. Nevertheless, we agree with the reviewer that these should be investigated and tested in an ideal world, and have discussed this important point in our discussion section.

7) In the Results section on page 6, the authors may want to describe why after delineating three clusters, they further subdivided cluster 2, and only cluster 2, into three subgroups. Does Figure 1 contain an error? Cluster 2 is divided into 3 subgroups, subgroup 1 with better social function, longer duration and moderate severity and subgroup 2 with short duration of pain, however looking at the table, subgroup 3 the duration of pain appears to be 50, is this years or months, compared with subgroup 1, 9.6 years, subgroup 2, 1.8 years therefore subgroup 3, does not have a short duration of pain. Perhaps there is an error in the Table? Again, in subgroup 3, it seems odd that the worst pain intensity was 1.6, whereas the average pain intensity was a 10. Is there an error?

Also, subgroup 3 supposedly had the worst current pain. Is this derived from the EHP pain? What about the McGill

Response: We are grateful to the reviewers for pointing out some typographical errors in the subgroup table which have now been rectified. We have also relabelled the original three clusters to make it clear that the largest cluster to the left of the dendrogram (relabelled Cluster 1) is the one that has been subdivided into three further groups and have given an explanation in the text. Worst current pain is derived from the McGill pain questionnaire.

8) On page 7, the authors present in Table 2, the site and presence of adhesions, however the adhesion scoring system that was used includes a number of other features, including density and length of adhesion. Were these relevant to any of the cluster analysis and is there a reason why the distribution of density or length of adhesion was not included in the table? Why include Table 2?
Response: We included Table 2 to inform the readers of the distribution of adhesions. We already stated in our results that only 3 women who had adhesions were graded as severe and extensive, one in each cluster, and hence has not included this information again in the Table. However, if the referee and the editor felt that we should remove this Table, we will do so. We will be guided by you.

9) On page 7, second paragraph, the word "ironically" should be removed from this sentence. More objective would be to state the evidence; pro and con from the literature. It also reflects a degree of naiveté about the etiology of pain in patients with chronic pelvic pain in general and adhesions specifically. Again in the first paragraph of the Intro, the word "ironically" should be removed. Other studies have demonstrated no correlation between locations or density of adhesions and pain and no response to adhesiolysis.

Response: We have removed the word ‘ironically’.

11) The statement "we did not find a correlation with the nature of pain and the site or type of adhesions" should be clarified. What is meant by "the nature of pain"? Are the authors referring to the severity of pain, the duration of pain, and other associated pain features?

Response: We indeed are referring to the severity, duration and intensity of pain as documented by patients in their questionnaires. We have now clarified this on page 9, lines 246-247).

10) What are the authors referring to by the statement that they cannot exclude historical adhesions related episodic pain? Using the words historical adhesion related episodic as adjectives for the noun of pain obscures the meaning of the sentence. Did the authors mean that patients would have had severe pain that was related to adhesions more than 6 months prior to the administration of the questionnaire? This seems farfetched.

Response: We agree with the reviewer that the statement is rather farfetched. We have now removed that notion, and maintain the point, however that, the correlation between the reported current pain scores and that of most severe (r=0.34) or average pain experienced (r=0.44) in the last 6 months captured by the questionnaires to be low.

13) A conclusion that cognitive behavioral assessment has been advocated, yet is it not routinely used in the management of is true, however given the previous statement, "that traditional gynecological approach to history taking and management strategy will not be adequate for pain and expectation management", a more forceful conclusion is in order. In fact the literature is replete with examples of whereby history and evaluation of patients with chronic pelvic pain must include cognitive, emotional behavior and other physical assessments prior to embarking on surgical management.

Response: We thank the reviewer for their suggestion. We indeed agree completely with your suggestion and have now included the following in within the conclusion as suggested. ‘However, our cluster analysis highlights that women with CPP can present in quite distinct characteristics clusters. It is, therefore, high time we place due attention to the fact that history
and evaluation of patients with chronic pelvic pain must include cognitive, emotional behavior and other physical assessments prior to embarking on surgical management.'