Author’s response to reviews

Title: Serum Macrophage Migration Inhibition Factor For Diagnosing Endometriosis And Its Severity: Case-Control Study.

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Version: 1 Date: 29 Apr 2020

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Reviewer 1 (Júlio Cesar Rosa e Silva): Evaluation:

Why did the authors register an observational study on the Trials.gov platform if there was no intervention? Laparoscopy is known to be the gold standard diagnosis of endometriosis, so there was an intervention to be taken for confirming and differentiating the study group from the control group.

Abstract:

the accuracy data is not included in the abstract, it must be added. It was expressed as sensitivity, specificity, positive and negative predictive values. A statement about how we measured accuracy was mentioned in the statistical analysis (Accuracy was represented using the terms sensitivity, specificity, positive predictive value, and negative predictive value. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for MIF in diagnosing endometriosis.)

Introduction:
The authors describe in the first paragraph that endometriosis is an undetected disease after menopause and before menarche, this statement must be withdrawn.

Corrected not withdrawn
Also, it should contain the existing gap in the scientific literature regarding the existing biomarkers and the sensitivity, specificity, PPV and NPV.

Done

Patients and Methods:
This sentence must be corrected: "we included three hundred postmenstrual women in the childbearing period".

Done
Why was laparoscopy indicated for these patients? Since laparoscopy at this moment is only indicated for failure in clinical treatment or suspect that the endometriosis lesions are compromising the function of organs. Because it is the gold standard diagnostic tool for endometriosis and the accuracy of any investigational tool should be based on the accurate diagnosis of the disease of interest.

Why were the patients out of hormonal treatment for 3 months before surgery if it is only indicated in the failure of medical treatment? To alleviate any suspected effect of hormone on endometriotic foci that may affect serum MIF level and be sure the hormone is completely metabolized so the comparison with the control group not biased by hormone effect.

How were chronic diseases (autoimmune, degenerative or neoplastic diseases (e.g. chronic / ulcerative colitis, diabetes mellitus, rheumatoid arthritis, multiple sclerosis, asthma, suspicion of malignancy)) excluded? By history or any relevant investigation when needed.

Why were patients with bleeding tendency or active infection excluded? And chronic smoking patients or patients using painkillers were excluded? How was this assessed? Because MIF, a pro-inflammatory cytokine, has been implicated in the pathogenesis of multiple inflammatory disorders. Also, there are studies that proved significantly reduced serum MIF levels in patients with COPD associated with smoking. It was assessed by history, it was mentioned in the second paragraph of methodology (Each patient was subjected to informed written consent, detailed medical history, thorough physical and gynecological examinations….)

In the statistical description the following sentence is duplicated: For comparing categorical data, Chi-square ($\chi^2$) test was performed.

Results:

The authors do not describe in the results the accuracy of MIF in detecting endometriosis. It was expressed as sensitivity, specificity, positive and negative predictive values.

Was a comparison made between the initial stages of endometriosis and the control group? (table 3).

No, it was made between endometriotic patients as a whole and the control group as a whole to detect if there is a difference. Then we made a comparison between serum MIF in different stages to detect if it increases (or decrease) by the stage of the disease.

This comparison is essential since the main objective in the search for a biomarker for endometriosis would be related to the initial stages of the disease because in the most advanced stages imaging tests are highly accurate.

In our study the aim was to detect the accuracy of serum MIF in general, and we included patients of all stages of the disease. May be in future study we can assess the accuracy in differentiating early disease from other causes of pain and infertility.
Table 3 needs to be better presented.
We can’t understand what do you mean by (better presented). If you would please specify, we could change accordingly. Meanwhile we have removed the subgroup analysis from that table and kept it written as a paragraph only.

Why do the authors describe the mean and median of MIF results?
We thought by that we could represent all the descriptive items to make it most informative to the reader.

Discussion:

The first two paragraphs should be removed or placed in the introduction.
Removed
The third and fourth paragraphs are confusing and do not show relevant data or should be placed in the introduction.
Third paragraph removed

Do not repeat data already exposed in the results.
don and revised

Reviewer 2 Antonio Simone Laganà, M.D. :
- Manuscript should be further revised by a native English speaker.
  Done
- I strongly suggest reporting not only the p values but also the corresponding confidence intervals.
  Done
- What are the actual clinical implications of this study?
  Done
- I would discuss these points in the light of new theories about the pathogenesis of endometriosis, referring to: PMID: 28571791; PMID: 29743986; PMID: 32046116; PMID: 32046558.
  Done
- The most common clinical signs of endometriosis are menstrual irregularities, chronic pelvic pain (CPP), dysmenorrhea, dyspareunia and infertility. Symptoms of endometriosis often affect psychological and social functioning of patients. For this reason, endometriosis is considered as a disabling condition that may significantly compromise social relationships, sexuality and mental health. I truly think that this manuscript should deserve at least few lines to stress this point of paramount importance. Authors may refer to: PMID: 31755674; PMID: 31755667; PMID: 28553145.
  Done
- I would suggest to stress the novel piece of evidence regarding the role of M1 and M2 macrophages, and of macrophage-induced apoptosis, in the pathogenesis of endometriosis (refer to: PMID: 31663401; PMID: 31717614; PMID: 27628753.
  These are really valuable comments, but we think is not applicable to our paper as it is not a review article. We focused on the methods to diagnose endometriosis, not symptomatology, pathogenesis or psychological and social impact of the disease. We think adding these paragraphs
will not add much to our paper and would make it too long for the reader. However, we revised the proposed articles and hope could make a review article in the near future.