Rio de Janeiro, Brazil

October, 2018.

Response to reviewers:

“Challenges in the diagnosis and treatment of gestational trophoblastic neoplasia worldwide”

Reviewer #1:

1) The authors shared their point of view on current approach to assessment and treatment of patients with GTD with different stages. This "editorial" is original, clear, and understandable. Probably, if they could add a table of algorithm summarizing the modern treatment of GTD.

REPLY: *We agree with the reviewer and we added a figure 1 in the text.* (Clean version, page 15, line 11).

Reviewer #2:

1) I have completed the review of the manuscript titled "Challenges in the diagnosis and treatment of gestational trophoblastic neoplasia worldwide". The authors should be congratulated for this high quality review. The manuscript is well-written with adequate reference to the current medical literature in the field. The content of the text is satisfactory enough and the tables are informative. The review can be published for educational purposes especially for clinicians in the field.

REPLY: *We would like to thank the reviewer for the assessment.*

Reviewer #3:

1) The manuscript is good written. The authors made a good study about the challenges of GTN diagnosis and treatments. However, I suggest the following:

A) Make a critical and short statement at the end of the abstract about the conclusion of the overall review work on the GTN disease problem that was attended by the revision manuscript. It can help to attract the attention of readers.

REPLY: *We agree with the reviewer and we added a short statement at the end of the abstract:* "The early diagnosis of this disease and the appropriate treatment avoid maternal death, allow the healing and maintenance of the reproductive potential of these women." (Clean version, page 3, lineS 24-25).

B) Include general and basic concept of the pathology of GTN disease to better understanding by non-expert readers.

REPLY: *We agree with the reviewer and we added a general and basic concept of the pathology of GTN before to present the hot topics to better understanding by non-expert readers:*

"THE BASIC OF GTD PATHOLOGY

The commonest forms of GTD are complete and partial molar pregnancies. Their cytogenetic origin derives from an abnormal fertilization. In cases of complete hydatidiform mole, the oocyte loses its DNA, being fertilized by 1 spermatozoa with diploid genetic load, or by 2 haploid spermatozoa - generating a diploid parthenogenetic zygote. In the cases of partial hydatidiform mole, the oocyte has conserved its DNA, being fertilized by 1 spermatozoa with diploid genetic load, or by 2 haploid spermatozoa - generating an zygote with a diandric triploidy. Women with complete

hydatidiform mole may develop postmolar GTN about 20-25%, while only 1-5% of women with partial hydatidiform mole will present malignant lesions.

The presence of chorionic villi in the myometrium, with or without vascular invasion, characterizes the invasive mole, the most common form of GTN. Usually its diagnosis is obtained through the uterine histopathology obtained by hysterectomy.

Choriocarcinoma is the most malignant and metastatic form of GTN. Although its primary lesion usually presents with great uterine invasion, in about 30% of the cases it crosses with distant metastases, notably in the lungs, liver and brain, by hematogenous dissemination.

Among the non-villous lesions that make up a GTN, PSTT and ETT are derived from the intermediate trophoblast. These clinical forms exhibit lower levels of hCG relative to invasive spring and choriocarcinoma. In addition, the therapeutic response of PSTT and ETT to chemotherapy alone is limited, requiring hysterectomy to maximize cure rates." (Clean version, page 6, line 10 until page 7, line 5).