Authors’ reply

Sir, We thank Martin Hirsch and colleagues1 for their interest in our study2 and for pointing out a degree of mismatch between our reported findings and the information on the ISRCTN database. The primary outcome of pelvic pain was operationalised more specifically as cyclical pain in the trial, and unfortunately, the secondary outcome of dyspareunia was inadvertently omitted from those listed in the ISRCTN entry. However, we can confirm that the trial outcome variables did not alter during the course of the study and all of the outcomes reported are reported in the final publication—no selective reporting occurred.

We are very pleased that the core outcome set for endometriosis, which the design of our study predated, is now available.3 The development of core outcomes plays a crucial role in establishing consensus on appropriate measures of treatment effectiveness and greatly assists comparison and synthesis—and, where applicable, statistical pooling—of trial results.4,5 We note that although pain, quality of life, pregnancy and adverse events were recorded in our study, other of the core outcomes related to birth (e.g. gestational age, birthweight and neonatal mortality) and patient satisfaction were not recorded and therefore not reported. Future trials in endometriosis will now be able to profit from the clear guidance provided by this set of core outcomes, and our understanding of the effective management of this condition will be enhanced accordingly.

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Authors’ reply

Sir,
Thank you kindly for the opportunity to respond to the letter from Dr Amorim and her colleagues.3 We would like to thank Dr Amorim and her team for their interest in our study2 and their invaluable observations.

We acknowledge that our series is small and heterogeneous. Our patients ranged from 20 to 37 weeks of pregnancy and only in one case did the pre-eclampsia-like (PE-like) syndrome resolve spontaneously and without being delivered. We, therefore, cannot affirm that all cases were PE-like syndrome, as we acknowledged in our article.

Although early and late pre-eclampsia (PE) may not have the same pathological pathways, they do share the same diagnostic criteria.3 We agree with Dr Amorim and her colleagues that the soluble fms-like tyrosine kinase-1 to placental growth factor ratio (sFlt-1/PlGF) and mean uterine artery pulsatility index (UtAPI) are generally predictive of early forms of PE; nevertheless, their negative predictive value before 37 weeks of gestation is extremely high (>97% for sFlt-1/PlGF <38) to exclude PE.4,5 For these reasons, we consider that there is no reason to believe that sFlt-1/PlGF is not a good tool to exclude the diagnosis of PE in the context of COVID-19.

Dr Amorim proposes that pre-eclampsia may act as a risk factor for developing severe or critical COVID-19. We would recommend being cautious about this statement, as there is no evidence published to date supporting this hypothesis and, in our series, the timeline of signs and symptoms is clear: COVID-19 pneumonia occurred prior to features of pre-eclampsia. Nevertheless, we do agree with Dr Amorim and her colleagues that our study is a small series and further research is needed to better understand the relation between PE and COVID-19. For this reason, we are very much looking forward to finding out the results of Dr Amorim’s study. Meanwhile, we believe that patients with signs and symptoms of PE in the context of severe COVID-19 should be managed with caution, as, in some cases, these signs and symptoms could be caused by COVID-19 and sFlt-1/PlGF might be helpful in the management of these pregnancies, especially in preterm cases.

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Re: Pre-eclampsia-like syndrome induced by severe coronavirus disease 2019: a prospective observational study

Sir,

We carefully read the work by Mendoza et al., a prospective observational study including 42 women, eight with severe and 34 with non-severe coronavirus disease 2019 (COVID-19) pneumonia. Six women presented signs and symptoms of pre-eclampsia and were assessed with uterine artery pulsatility index (UtAPI) and angiogenic factors (soluble fms-like tyrosine kinase-1/placental growth factor [sFlt-1/PIGF]). Only one woman had abnormal sFlt-1/PIGF and UtAPI and symptom resolution occurred in two women who remained pregnant after recovery of pneumonia. The authors concluded that pregnant women with severe COVID-19 can develop a pre-eclampsia-like syndrome that might be distinguished from actual pre-eclampsia by sFlt-1/PIGF, LDH and UtAPI. We believe that this conclusion deserves comments.

First, although we agree that COVID-19 may mimic the inflammatory pattern observed in pre-eclampsia, once both diseases are thought to be accounted for by systemic inflammation, this rationale may only explain the clinical course of the two women with disease resolution, but not the others. Second, not all pre-eclampsia cases are the same. Early- and late-onset pre-eclampsia have distinctive features, pathogenesis of these two situations differs and markers such as UtAPI and sFlt-1/PIGF can be predictive of early but not late-onset pre-eclampsia. Therefore, based on the available evidence, we do not believe that these markers can be used to rule out pre-eclampsia in the context of COVID-19 infection. The two women who recovered were in their second trimester (20 and 24 weeks of gestation) and presented with severe pneumonia, so they may have had a pre-eclampsia/HELLP (haemolysis, elevated liver enzymes and low platelet count) -like situation, associated with the COVID-19 inflammatory state and the intensive care unit interventions. The other women who delivered cannot be ruled out as pre-eclampsia cases only by these markers and their gestational ages were significantly higher (28, 30, 36 and 37 weeks of gestation).

The topic is remarkably interesting and must be addressed, but six women is still an exceedingly small sample from which to derive any robust conclusion on the matter. It is likely that both phenomena may occur in the clinical setting of obstetric patients at risk of COVID-19 infection: namely, COVID-19 mimicking pre-eclampsia, particularly in early pregnancy and already established pre-eclampsia acting as a risk factor for developing severe or critical COVID-19. These two separate clinical conditions need to be investigated when caring for women at risk of each one or both, based on clinical and epidemiological criteria. Adequate diagnostic tools to differentiate between them would be helpful, but to our knowledge UtAPI and sFlt-1/PIGF do not have scientific support or have not been thoroughly investigated to respond to this need.

We are now collecting data within a cohort study that has already enrolled 181 Brazilian pregnant and postpartum women with confirmed severe acute respiratory syndrome coronavirus 2 infection and, so far, the association with hypertensive disorders of pregnancy seems remarkable. We hope that our data may improve the knowledge about the potential bidirectional relationship between pre-eclampsia and COVID-19. However, the question that remains to be clarified is who came first, the chicken or the egg. And the answer will probably be different in each woman.

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