Author’s response to reviews

Title: The effects of spinal anaesthesia for elective caesarean section on uterine and umbilical arterial pulsatility indexes in normotensive and chronic hypertensive pregnant women: an observational study.

Authors:

Luís Guedes-Martins (luis.guedes.martins@gmail.com)
Helena Graça (lena.graca@gmail.com)
Joaquim P Saraiva (saraivajp@hotmail.com)
Luísa Guedes (luisa_ferraz@hotmail.com)
Rita Gaio (argaio@fc.up.pt)
Ana S Cerdeira (ana.cerdeira@gmail.com)
Filipe Macedo (filipe.macedo@hsjoao.min-saude.pt)
Henrique Almeida (almeidah@med.up.pt)

Version: 2
Date: 5 July 2014

Author’s response to reviews: see over
Cover Letter

Name of Corresponding Author: Luís Guedes-Martins, MD
Manuscript Title: The effects of spinal anaesthesia for elective caesarean section on uterine and umbilical arterial pulsatility indexes in normotensive and chronic hypertensive pregnant women: an observational study.
MS ID: 1639466618124671

Dear Editors,
BMC Pregnancy & Childbirth

We would like to thank you and the reviewers of BMC PREGNANCY & CHILDBIRTH for taking the time and effort to review our manuscript. The response to reviewers’ remarks is attached to this letter, after being approved by all authors. We hope it is addressing all raised concerns and will be looking forward to your response.

Yours sincerely,

Signature

Date

July 5, 2014

Luís Guedes-Martins, MD
Centro Hospitalar do Porto, EPE
Departamento da Mulher e da Medicina Reprodutiva
Largo Prof. Abel Salazar 4099-001 Porto
Department of Experimental Biology
Faculty of Medicine, University of Porto, 4200-319 Porto
Portugal
E-mail: luis.guedes.martins@gmail.com; Ph: +351-965130529
Editorial Comment

"This is a commendable study which has relevant clinical and scientific interest for obstetricians and obstetric anesthesiologists. Please review the comments of all reviewers, particularly reviewer 2. There are some key aspects of the study design that will need to be commented on, especially the choice of a chronic hypertension comparator group and the discrepancy in the number of patients in each group. Brief commentary on the uterine vascular reactivity that affects hypertensive patients in the discussion would also be worthwhile. The figures also require revision (see reviewer 3 comments).

AUTHORS’ REPLY: The authors are most grateful to the reviewers for their useful comments to our manuscript. We have carefully addressed all comments and suggestions point-by-point.

1. The choice of a chronic hypertension comparator group was clarified;
2. The discrepancy in the number of patients in each group was justified;
3. Uterine reactivity that affects hypertensive patients was commented;
4. Figures have been improved.
Reviewer: 1
Stephen Halpern

Reviewer’s report:
The purpose of this study was to determine the effect of spinal anesthesia on uterine and umbilical blood flow in normal and hypertensive patients undergoing elective cesarean section. The primary outcome was the change in pulsatility index for the uterine arteries and umbilical arteries. The authors found that the mean arterial blood pressure fell significantly in both populations after the induction of spinal anesthesia. In normal women, the pulsatility index of neither the uterine arteries or umbilical artery changed. However in hypertensive women, there was a decrease in the uterine artery pulsatility index. The authors conclude that, in hypertensive patients the impedance in the uterine arteries is reduced. In general, the study is well designed and well written. The question is well defined and the methods are appropriate. I am not in a position to comment on the analysis of this work, a statistician should be asked for their opinion. The purpose was to determine the effect of spinal anesthesia alone. This is very difficult considering, in the real world, vasopressors are commonly used but in this study patients that require vasopressors were eliminated.

Comments:
Discretionary Revisions
1) The classical teaching is that the placental bed, and therefore the uterine arteries are fully dilated, yet in the hypertensive patients, further dilation seems to be possible. This may, in fact improve the outcome of the fetus in patients with severe hypertension (see BMJ 2009;102(3):369-78). This may be a worthwhile discussion point.

AUTHORS’ REPLY: Thank you for your comments. This precious study (Ginosar Y et al., 2009) points out that antepartum continuous epidural therapy reduces uterine artery resistance in pre-eclampsia <32 weeks. Although, our study focused on pregnant women with chronic arterial hypertension, the value of the report is high and so, it was added to the revised manuscript. (lines 559-562, page 23, revised version)

Minor Essential Revision
2) Please report neonatal outcomes (cord gases, Apgar scores). Do these correlate with changes in pulsatility index?

AUTHORS’ REPLY: This study was conducted in a sample with normal pregnancy outcomes. For this reason, any relationships between Apgar scores and the investigated indices were not explored. For the same reason, and because it is not a routine practice in our clinic, cord gases were not measured. Still, upon your suggestion, Apgar score <7 at 5’ was added. (Table 1, page 30, revised version)

Discretionary Revision
3) It seems to me that the pulsatility index may be dependent on the side on which the placenta is located. In the hypertensive patients, was the pulsatility index decreased on the placental side as well as the non placental side?

AUTHORS’ REPLY: Thank you again. As I am not sure about the vessel that is being mentioned, I answer the question for both umbilical and uterine arteries separately.

Umbilical artery. It is well known that umbilical artery ratios are significantly higher at the fetal end of the cord when compared to ratios at the placental cord insertion. But, in our study, the umbilical artery Doppler flow spectrum was recorded at a free cord loop. Measurements on the umbilical placental site/non placental site were not performed. (See Doppler flow assessment section, page 8-9, revised section)

Uterine arteries. For uterine arteries impedance analysis, mean UtA-PIs were considered. It is not possible always refer the placental location to one side of the uterus as nearly 60% of placenta in uncomplicated pregnancies are located centrally (Ito Y et al., 1990; Hernandez-Andrade E et al., 2002). Other authors mentioned that the slight tendency of laterality in central placenta might be used to define the placental side location; however, in 40% of complicated pregnancies it was still not possible to establish with certainty a specific side tendency in the placental location (Ito Y et al., 1998; Hernandez-
Andrade E et al., 2002). In our study, it was possible to clearly locate the placenta in one side of the uterus only in 39% of the cases (91/236). Additionally, patients with unilaterally abnormal uterine artery pulsatility, but normal mean PI, did not seem to be at increased risk for obstetric and perinatal complications, irrespectively of placental location (Contro E et al., 2010). Unfortunately, this analysis was not possible.

Refs:


Reviewer's report:
You should be congratulated for a study with a large number of subjects and has been carefully done.
Major essential:
You need to identify better why your paper is novel. I think you erred by missing out looking at preeclampsia, only chronic hypertension, which I think is a big shame as this is the group that previous research suggests to have the biggest difference from normal pregnancy, while chronic hypertension and normal pregnancy had little differences when you look at % change from baseline in these ultrasound indices. Please include discussion of the relevant literature (see below). Please shorten the intro and discussion and bibliography - make it more focussed and relevant to the specific question.

AUTHORS’ REPLY: Thank you for your comments. Actually we have not studied pregnant women with preeclampsia yet. However, we are now looking at the subject more closely and expect to address it in the near future. The literature suggested was included and the introduction/discussion were shortened.

Minor essential:
Please amend the title to specify normal pregnancy and chronic hypertensive.

AUTHORS’ REPLY: The title was amended according to your suggestion.
(lines 1-3, page 1, revised version)

L62 Bupivacaine and sufentanil are not proper nouns and do not need capital letters in the middle of a sentence.

AUTHORS’ REPLY: The mistake was corrected.

L79. A major challenge ...
L79. I disagree with this sentence. There are two separate disease entities here – a) chronic hypertension which may or may not have superimposed preeclampsia/PIH and b) pre-eclampsia/PIH in a previously healthy patient. The use of the word "superimposed" implies the former, whereas the latter is probably more common, depending on maternal age, parity and other risk factors.

AUTHORS’ REPLY: Thanks again for your remark. The term "superimposed" was removed.
(lines 78-82, page 4, revised version)

L83. Over the last X period of time ....
L84-89. Not sure how relevant this entire passage is for the paper. Consider removing or shortening it.
L89-94. Also superfluous; this is not an OB anesthesia review.

AUTHORS’ REPLY: The referred sentences were substantially shortened.

L98 neuraxial blockade
L99 occur or result rather than establish

AUTHORS’ REPLY: Thanks again for your suggestion. The corrections were made.

L100-103 I think you must mention here the study by Ramos Santos et al: The effects of epidural anesthesia on the Doppler velocimetry of umbilical and uterine arteries in normal and hypertensive patients during active term labor. Obstet Gynecol. 1991 Jan;77(1):20-6. Like you, they found that uterine artery impedance (there the SD ratio) fell while the umbilical artery impedance was unchanged. However, unlike your study, this finding was observed only in women with preeclampsia. By comparison, women with chronic hypertension and normal pregnancy had no changes in either umbilical or uterine artery. This study is critical for both the introduction and the discussion. This is a well-known, classic study and should have provided the background to yours and your results should be interpreted with reference to it. This was an epidural analgesia rather
than a spinal anesthesia study, but it deals with sympathectomy. There are other early studies also from Alahuhta's group from Finland and others.


Plus a whole load of normal pregnancy studies:


The point I am trying to make is that you should demonstrate what your study offers that is different from these earlier studies.

AUTHORS’ REPLY: We acknowledge your observation. Indeed, we are aware of these investigations, namely that it was carried out by Ramos-Santos et al., 1991. Unfortunately they are not comparable with our study: (1) all refer to epidural anesthesia (Ramos-Santos et al., 1991; Alahuhta et al., 1993; Alahuhta et al., 1991; Hughes et al., 1990; Morrow et al., 1989; Patton et al., 1991); (2) S/D index is not comparable to PI (this comparison, if it were established, would be viewed with extreme criticism by any obstetric sonographer) (Ramos-Santos et al., 1991; Morrow et al., 1989; Patton et al., 1991); (3) pathological pregnancies were not considered in this study (Alahuhta et al., 1993), and (4) our Doppler measurements were performed in the absence of labor (Ramos-Santos et al., 1991; Hughes et al., 1990; Patton et al., 1991).

However, despite these differences, your recommendations led us to review the context of Introduction and Discussion sections and integrate the Ramos-Santos et al. study.

L130 To what does [N/ REF.* 133/10(086-DEFI/126-CES] refer? Was the study registered with a registry like clinicaltrials.gov of NIH?

AUTHORS’ REPLY: This is a reference that corresponds to the certificate of study acceptance by the local ethics committee of Centro Hospitalar do Porto. The study is not registered in clinicaltrials.gov of NIH.

L132-6 Can you make this two or more sentences – here the verb is four lines after the start of the sentence. May be easier just to write: "Inclusion criteria were: ... "

L137-143 Better to write: 'Exclusion criteria were : ... "

AUTHORS’ REPLY: We appreciate your suggestions. The paragraphs were reformulated. (lines 132-139, page 6, revised version)

L167 Not critical, but why L2/3 as routine? We miss diagnose this level frequently (Bromage).

AUTHORS’ REPLY: All anesthetic procedures were performed by the same OB anesthesiologist. In fact, the level of neuraxial blockade was based on his option.

L170 Please specify if this was hyperbaric or isobaric bupivacaine.

AUTHORS’ REPLY: Was used hyperbaric bupivacaine. We specified that in the text, section «Spinal anaesthesia for elective caesarean section».

L175 At what time was T4-6 sensory level required?

AUTHORS’ REPLY: The Doppler flow evaluation of right and left uterine and umbilical arteries was performed immediately before spinal anaesthesia performance (first time point) and after blockade was
achieved (second time point). The time from the first to the second Doppler acquisition was dependent on the time necessary to achieve anaesthetic blockade (~5 minutes). Although not exactly the same for all the patients, it was similar since only the procedures considered technically easy and uneventful were eligible for the study. This is a study limitation that was rigorously discussed in the revised version. (See Study limitations section, lines 418-429, page 17-18, revised version)

L176 Please specify by what method BP was assessed. It seems as if this was by manual auditory phynometer technique rather than using automated oscillometric technique. Please confirm and explain the reason.

AUTHORS’ REPLY: Blood pressure (BP) was recorded with an automated instrument (GE Healthcare Carescape™ V100 Vital Signs Monitor w/ DINAMAP Blood Pressure) at 2-min intervals from induction to delivery. Manual auditory phynometer technique is not current practice in our institution. (See Blood pressure assessment, lines 177-178, page 8, revised version)

L183 Why ephedrine? Ngan-Kee's research and others have demonstrated very well that phenylephrine or a similar alpha-agonist is associated with less foetal acidosis and is the drug of choice. This point is not critical to the study but will irritate any OB anesthesiologist reading this paper.

AUTHORS’ REPLY: Thank you for your review. The term ephedrine has been replaced throughout the manuscript for ‘vasopressors’ (VP). The reason we prefer ephedrine instead of phenylephrine is because it is less expensive. However we recognize your comment according to the evidence-based medicine.

L187 Uterine artery blood flow can be quite difficult to assess transabdominally in many women – particularly in obese women. It typically takes time. Here you measured it bilaterally, as well as umbilical artery (easier). This is fine for baseline but to what degree did this affect the timeline of your second measurement?

AUTHORS’ REPLY: This is a study limitation that was mentioned in the revised version. However, all Doppler measurements were made by a researcher with extensive experience in Doppler ultrasound. No more than two minutes was required for the acquisition of the waveforms of both uterine arteries and umbilical artery (recorded from a free cord loop). Additionally, the sequence of measurements was extremely accurately and always in the same order: in first the right uterine artery, in second the left uterine artery, and finally, the umbilical artery. (See Doppler flow assessment). Technical difficulties to obtain the pulsatility index of uterine/umbilical arteries were an exclusion criteria (see Results section & Study limitations section).

L214 Please expand on this sentence – I do not understand it. I am not sure why you used modelling and I am going to have to ask for a statistical consult to check this approach.

AUTHORS’ REPLY: We are grateful for your interest. Please see the responses to reviewer 3 (comments about statistical aspects of the paper).

L272-277 Probably better to include a CONSORT-like flow chart (even though this was no a randomized trial).

AUTHORS’ REPLY: We understand your comment. However, this is not a randomized study, and for this reason, we decided to preserve the original paragraph.

L283 …were non-smokers.
L285 Weeks do not require 2 decimal points.
L286 If you state that something is statistically significant, please present the data in the text (means, mean difference, 95% CI, p-value).

AUTHORS’ REPLY: Thanks again for your suggestion. The corrections were made.

Table 1. Some demographic variables surprise me, like menarche, 1st sexual intercourse, educational level. What was the rational for these factors?
AUTHORS’ REPLY: Thanks for the remark. The variables 'age at menarche' and '1st sexual intercourse' were removed. Indeed, our hospital covers an area with important socio-economic difficulties which are reflected in the ‘educational level’ variable of the sample.

Figure 2. Does not look a particularly impressive effect on uterine artery PI after spinal anesthesia. Am I missing something? As you used paired t tests, why not represent the data graphically as % change from baseline for NT vs HT groups (as bars).

AUTHORS’ REPLY: There are significant changes for the hypertensive group from the values obtained after spinal anesthesia, as the confidence intervals for the mean prediction do not overlap – Figure 2. We have not used t-tests. The comparisons amongst different time points, vessels and hypertensive status are all done at once, via the regression model.

The discussion is far too long. It should focus on two areas a) limitations of the study results in view of the methodology and b) interpretation of the results in the context of relevant literature. Less is more.

AUTHORS’ REPLY: Thank you again. The discussion was shortened.

L364 "…. e pregnant…" In this era, an e pregnancy sounds appealing but I guess this is a typo.

AUTHORS’ REPLY: Yes, this is a typo.

L371. But you did not assess severe preeclampsia or preeclampsia, rather chronic hypertension, probably a very different entity.

AUTHORS’ REPLY: The paragraph was eliminated from the manuscript revised version.
Reviewer's report:
This is a nice study with appealing statistical modeling. It should be published.
Here are some details to polish in the revised version:
The dis-balance between number of low-risk and hypertensive pregnancies is quite large, according to the figures on page 3 (lines 58-59). It should be mentioned somewhere in the discussion – and also in the Study limitations section.

AUTHORS’ REPLY: We agree with the referee and followed his suggestions. A new sentence was added in the “Discussion” and in the “Study limitations” sections. (lines 406-413 & 431-434, page 17-18, revised version)

On page 10, we find the sentence “Graphical analyses confirmed that 249 the variance function models were successful in accommodating the error heteroscedasticity.” without knowing what variance functions were used, exactly. It is probably the variance function implied by the mixed (heteroscedastic) model, but that should be stated explicitly.

AUTHORS’ REPLY: Thank you for the raised point. The model for PI considered different variances for each vessel while the model for MAP considered different variances for each time point (before/after). The information for the PI-model was missing and was now included on page 10 (revised version).

Multivariate analysis heading on page 13 (line 305) is probably not more multivariate than the multiple regression is. The heading should be replaced.

AUTHORS’ REPLY: The heading was replaced and, accordingly, “multivariate” was replaced by “multiple” in two other instances (pages 9 and 13).

Figures 1 and 2 are very hard to read (even after the jittering). To tell the truth, I cannot see the confidence intervals there at all. The authors should consider redrawing them using a more suitable graphical form (e.g. boxplots, or even better, separate histograms, etc. for the fitted values and then segments corresponding to different confidence intervals in the style of plot(intervals(object)) from nlme R package).

AUTHORS’ REPLY: We agree with the referee and have re-drawn the figures, hoping that they have become clearer. We deleted the horizontal bars flagging the statistical significances at the top of the figure, and created a higher distance between the observed values and the confidence intervals for the mean prediction. We thank the reviewer’s suggestion about other graphical forms but we would like to maintain our original version of the plots.