Author’s response to reviews

Title: Elastography in predicting preterm delivery in asymptomatic, low-risk women: a prospective observational study.

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Author’s response to reviews: see over
Dear editorial board of BMC Pregnancy and Childbirth.

Please find enclosed the revised manuscript: “Elastography in predicting preterm delivery in asymptomatic, low-risk women.” by Slawomir Wozniak et al. We are very grateful for the punctilious and helpful reviews. We did our best to follow all the suggestions of the reviewers. Please find below our answers to all the points that the reviewers had raised. We believe that after implying the suggested changes the manuscript was substantially improved. Once again we would like to thank the reviewers for the time and effort taken to review our study.

Sincerely yours,

Piotr Czuczwar and Slawomir Wozniak on behalf of the authors.

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Revision response:

Reviewer 1:

How reproducible is this color code method?

Our method is based on the technique used by Swiatkowska-Freund and Preis (2011, ref 11). The authors suggested that due to the technical aspects of this technique (no additional force applied, elastographic images generated by patients breathing movements and arterial pulsation) the interobserver variability should be decreased. But no reliability studies have been performed so far and it is stressed in the discussion section. Moreover, as discussed in
the Discussion section, we focused on the internal os, and it has been previously shown that this region is relatively independent of inter and intraobserver variability (but by using different elastographic techniques, so these results cannot be extrapolated to ours) (Hernandez Andrade et al., 2013; Molina et al., 2012; ref 16 and 26). Therefore it can be speculated that elastographic assessment of the internal cervical os, due to the anatomical conditions, may be reproducible, but naturally reproducibility studies for our technique are mandatory and we are collecting data for such study.

**Which is the Kappa value for assigning the same color code by different operators?**

Our study is the first investigating the possible usefulness of elastography in predicting preterm delivery. We were aware of the reproducibility issues (discussed in the reply to the previous question) and to overcome them, for the purpose of this study we decided, that all examinations will be performed by only one examiner, and therefore it is not possible to calculate the Kappa value for different operators. We hope that our results will encourage other groups to continue research in this field and to clarify the reproducibility issues. As mentioned above, we are collecting such data at this moment, hopefully similar data for other elastographic techniques will be published to allow comparisons between various elastographic techniques.

**How the operators decide which the best image for evaluation is?**

For the purpose of publication we had to use still images. However, elastography is a dynamic examination and therefore is best viewed and interpreted on video sequences. Due to the technical aspects of this examination any additional movements (patient changing position, coughing or even talking; the operator moving his hand) lead to the presence of artifacts and may completely change the appearance of the color map. That is why the goal of this examination was to obtain a stable image without any additional movements with a stable color map. Once a stable video sequence was obtained (at least 10 seconds) the operator decided about the dominant color of the internal cervical os, in case of difficulties (two colors of similar intensity visible) the softer option was noted. A sentence explaining this technique in detail was added in the M&Ms.

**According to Table 1 there were no cases with short cervix; do the authors have any comment on this?**

One of the inclusion criteria for our study was cervical length > 25 mm. That is why in our studied population the shortest cervix was 27 mm. We stressed in the title and objectives of our study that we focused on low-risk, asymptomatic women. Because the results of cervical screening are not very reassuring (many women with normal cervix length in the second trimester still deliver preterm (Iams et al., 1996)) we tried to find a technique that might
identify patients with high risk of preterm delivery in the low-risk population and improve
the efficacy of screening for such cases. Elastography seemed a perfect tool for this purpose,
as it seemed reasonable to assume, that the changes in internal os stiffness should precede
dilation.

**Was there any association with cervical length?**

We calculated the correlation between elastographic assessment of internal cervical os and
cervical length (Spearman correlation; \( r = 0.3594; p < 0.001 \)). In our paper, we decided to
show the correlation between elastographic assessment of internal cervical os and %cervical
shortening between 18-22 and 30 weeks and not with cervix length, because in our study we
included only patients with normal cervix length. We calculated the correlation that the
reviewer asked about, and added a short sentence about these calculations in the M&Ms
and in the results section.

The results show that most of women delivering before term had a soft internal
cervical os at 18 weeks of gestation. The false positive rate was very low as only 3 from
27 patients considered as having a soft cervix did not deliver prematurely. This is
very impressive as many other factors can be associated with preterm delivery or
complications appearing during pregnancy can also end in a spontaneous
preterm delivery.

We agree with the reviewer that the pathogenesis of preterm delivery is multifactorial, and
the screening cannot be based only on the assessment of the cervix, even though cervical
length is one of strongest predictors of preterm delivery [Goldenberg et al., 2008, ref 1]. For
the purpose of this study we decided to focus on a selected population of low-risk patients,
with the inclusion criteria designed to exclude the majority of other causes of preterm
deliveries. This explanation was added in the Discussion section.

**How was the association with preterm delivery before 32 or 30 weeks of gestation?**

In our study we wanted to focus on the low-risk asymptomatic population and that’s how we
prepared the inclusion criteria. The main goal of our study was to test, whether elastography
can improve the performance of cervical screening. That is why all patients included in the
study were classified as low-risk of preterm delivery at 18-22 weeks and it was unlikely that
they might deliver shortly after inclusion into the study. And indeed only one 1 patient
delivered at 31 weeks and 3 at 33 weeks, that is why it is not possible to assess the
association with preterm delivery before 32 or 30 weeks of gestation in our study population.

Elastography is certainly an emerging technique that can provide useful information for cervical evaluation; however, when no quantitative measurements are used, it is important to provide evidence that the qualitative analysis can be reproducible.

We definitely agree with the reviewer on this point and as mentioned in the answers to the previous questions we are gathering data for such study now. We are aware that this is the first report assessing the usefulness of elastography in SPD screening and these results will have to be verified in larger studies and in other centers. To minimize the effect of reproducibility issues we decided that all examinations would be performed by one experienced physician. We also hope that by showing the potential of elastography in screening for preterm delivery our study will inspire other groups to continue research in this field.

Reviewer 2:

The authors have mentioned about the less predictive value of cervical length screening. It has been recorded for all cases. Though not necessary, it may add to the value of elastography if they could add the corresponding values (of cervical length <25 mm) in Table 2.

One of the inclusion criteria for our study was cervical length > 25 mm. That is because while planning this study we decided to focus on women classified as low-risk of preterm delivery (basing on current recommendations) and the main objective of our study was to try to improve the performance of current screening for preterm delivery in the low-risk population. As mentioned in the Discussion section, many patients who deliver preterm had normal cervix length in the second trimester (Iams et al., 1996). That is why we thought it might be of interest to investigate the possible role of elastography in patients with cervix length > 25 mm. We agree with the reviewer, that it would be interesting to perform the elastographic assessment of internal cervical os in patients with short cervical length and we are collecting such data at this moment.
Reviewer 3:

The elastographic evaluation of the cervical tissue is still a novel method in obstetrics.

The aim of the study is innovative, as it is the prediction of preterm delivery in low risk asymptomatic women by measuring the internal cervical os stiffness at 18-22 weeks of gestation.

Methodology, statistical analysis and presentation of the results seem to be presented well. The significance of the results in daily clinical work is currently limited, because of the lack of standardization of the elastographic assessment of the cervical tissue. Nevertheless this study certainly includes cognitive values and is worth reading.

We agree with the reviewer that the main limitation of elastography is currently lack of standardization (Fruscalzo and Schmitz, 2012; ref 29) and it is discussed in the Discussion section and stressed in the paragraph about the limitations of our study. One of the aims of our study was to assess the potential of elastography in predicting preterm delivery. We hope that the results of our study will encourage other groups to further investigate this issue and help solve the standardization issues.

Once again we would like to thank for all the precious comments, and for the time and effort taken by the reviewers to review our study.