Cervical Remodelling Biomarkers to Predict Risk Of Preterm Birth

H Rosen O'Sullivan, N Suff, C Valensin, R Tribe, A Shennan
Department of Women's and Children's Health, King's College London

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Background

- Cervical remodelling is the common endpoint of all preterm aetiologies. (1)
- Cervical softening, the initial phase of remodelling, is detectable from early in the first trimester and continues until term. (2)
- Cervical softening can be measured in pregnancy using biomechanical tests (ultrasound elastography and the cervical consistency index) and has been shown to be predictive of spontaneous preterm birth (sPTB) (3,4)
- Matricellular proteins (MCP) are non-structural proteins within the cervical extracellular matrix which play a key role in the cervical softening process. (5)
- Mice deficient in MCP have phenotypic abnormalities including premature cervical softening (6)
- In this study we measure cervical stiffness (CS) in a cohort at high risk of preterm birth using an aspiration device (the Pregnolia device – Figure 1) and evaluate the relationship between CS values and risk of preterm birth.
- We also assess whether MCP can be detected in the cervicovaginal fluid (CVF) of pregnant women and if levels are different in those who deliver at term and preterm.

Methods

- Women at high risk of sPTB underwent serial cervical stiffness measurements at up to 5 predefined gestational timepoints
- Paired cervical length measurements, quantitative fetal fibronectin (qfFN) and biomarker swabs taken in a subgroup of women
- ROC areas used to evaluate cervical stiffness test as a predictive test for the primary endpoint (delivery <37 weeks)
- Multiplex immunoassays used to compare matricellular protein levels in CVF
  - at different gestational timepoints
  - in term (>37+0) and preterm samples (<37+0) from demographically matched participants, taken between 20-24+0 weeks
- Data analysed using GraphPad prism V.9

Eligibility Criteria:
- 1 or more sPTB 16+0-36+6
- Cervical length <25mm in current pregnancy
- Uterine anomaly
- Multiple pregnancy
- History of:
  - cervical surgery
  - full dilatation caesarean section

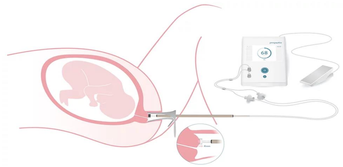


Figure 1 – The Pregnolia device

Results

- 136 participants were included. 60 of these women have delivered. 9 women had a spontaneous preterm birth <37+0 weeks and 51 women delivered at term ≥37+0 weeks. 4 women had an iatrogenic PTB and were excluded. CS measurements were well tolerated and there were no adverse events related to the test.
- CS measurements were significantly different between women delivering preterm <37 weeks and women delivering at term. Median CS for the preterm group was 35 mbar compared to 63 mbar for the term group, p=0.021 (Figure 2).
- CS was a good predictor of sPTB <37 weeks, with measurements taken between 20+0 to 24+0 weeks gestation having the best predictive value (AUC 0.81, 95% CI 0.58-1.00, p=0.04), and performing better than cervical length and fetal fibronectin in this cohort. (Figure 3)
- Trend towards lower CS values in those developing a short cervix (<25mm) later in their pregnancy (up to 24+0 weeks). Median CS in those developing a short cervix was 39 mbar compared with 64 mbar for those maintaining cervical length >25mm (P=0.09), (Figure 4).
- CS values were significantly lower in those with a transvaginal cerclage in situ (history or ultrasound indicated), compared to those with no intervention (median CS with TVC 48.5 vs median CS no intervention 69, p=0.034). Cervical stiffness values were significantly higher in those with a TAC in situ compared to those with a history or ultrasound indicated TVC (median CS TAC 128, median CS TVC 48.5, P=0.0008) and those with no cerclage (median CS TAC 128, median CS no cerclage 69, P=0.002). (Figure 5)
- Osteopontin, SPARC, Tenascin C and Thrombospondin 2 were detectable within the CVF at all gestational timepoints (Figure 6), and thrombospondin 2 and SPARC levels were loosely correlated with cervical stiffness measurements (Figure 7).
- Trend towards higher levels of Thrombospondin 2 and Tenascin C in the CVF of women delivering <37 weeks. (Figure 8)

Figure 2 – Preterm and Term CS values

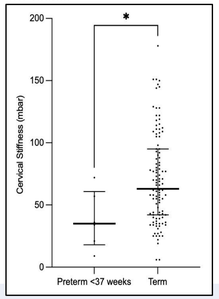


Figure 3 – ROC curve for CS, CL and qfFN as predictive tests for sPTB <37 weeks

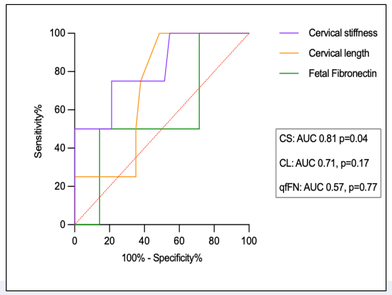


Figure 4 – CS values in those developing short cervix vs maintaining cervical length

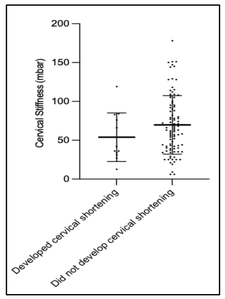


Figure 5 – CS values with different cerclage types

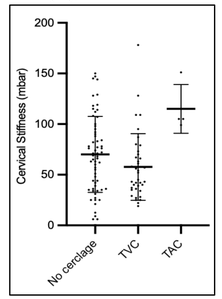


Figure 6 – Matricellular protein levels at gestational timepoints

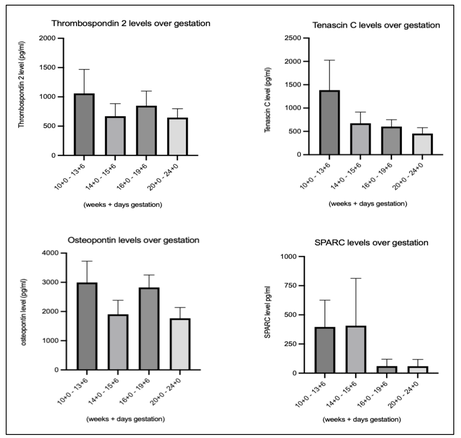
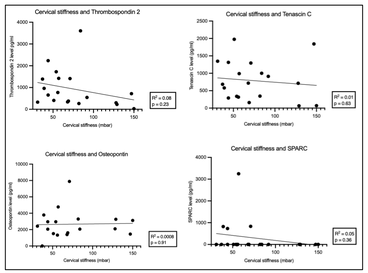


Figure 7 – Correlation between matricellular protein levels and cervical stiffness values



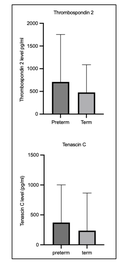


Figure 8 – Matricellular protein levels in term and preterm samples

Conclusion

- Cervical stiffness measurements taken using the Pregnolia device are a good predictive test for sPTB, and perform better than cervical length and fetal fibronectin in this cohort
- Combining cervical stiffness measurements with other parameters may help to improve prediction of sPTB
- Lower cervical stiffness values in women delivering preterm and in women requiring a vaginal cerclage suggests that cervical softening occurs with cervical shortening and is associated with risk of sPTB
- Higher cervical stiffness values in women with a TAC is an interesting finding and may provide insight into the potential mechanism of how these sutures work
- Matricellular proteins are detectable in human cervicovaginal fluid across all gestational time points
- There is a trend towards higher levels in the cervicovaginal fluid of women delivering preterm and this warrants further investigation
- More data required to further evaluate these biomarkers, and results will be reanalysed once the rest of the cohort have delivered

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