

## **Prediction of spontaneous preterm birth in multiple gestation by cervical elastogram**

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## Background

Preterm birth is the leading cause of perinatal morbidity and mortality in multiple pregnancy, and the medical and educational expenditure and lost productivity associated with preterm birth is very high.

The risk of preterm delivery in singleton pregnancy is 5-7%, and that in twin pregnancy is 7-8 fold higher than singleton pregnancy. [1] Identification of pregnant women at risk of preterm birth could allow intervention to reduce their risk. Treatment such as progesterone, cervical pessary, and surgical cerclage in selected cases have been shown to be effective measures to reduce the risk of preterm delivery in singletons. [2-4] Prevention of preterm birth in multiple pregnancy is more challenging. A lot of preventive methods studied, including bed rest, tocolysis, nutritional adjustment, cerclage and cervical pessary, have not been shown to be effective. [5-10] Until very recently, a study have found that vaginal progesterone is effective in reducing preterm birth < 33 weeks in twin pregnancy with a risk reduction of 30%, and a significant reduction in neonatal death, respiratory distress syndrome, and composite morbidity and mortality was also demonstrated. [11]

Premature dilatation and shortening of cervix have been demonstrated to be a very good predictor of preterm birth in singleton as well as twin pregnancies. [12-25] The ability to identify pregnant women with short cervix allows timely intervention to reduce their risk. Nevertheless, not all women who end up having preterm birth have a short cervix, prompting identification of other cervical signs to increase the prediction of preterm birth.

Recently, a new ultrasound technology called sonoelastography has enabled the measurement of tissue stiffness. [26,27] It has been widely applied in assessment of breast lump and liver cirrhosis, as the tissue is stiffer in case of malignancy and cirrhosis. [28,29] Sonoelastography is potentially useful for the objective assessment of cervical consistency which could be related to risk of preterm birth. A recent study has shown that strain in the internal cervical os has been shown to be associated with spontaneous preterm delivery in singleton pregnancies. [30] This study has shown some promising results in the use of elastography in prediction of preterm delivery, however, it is limited by the fact that the sonographic technique used is strain elastography, which could be affected by the pressure of the probe on the cervix. On the other hand, shear wave elastography creates images based on moving waves and is

therefore a dynamic technique to assess energy loss when it travels through tissue. The benefit being that the results are relatively independent of the operator, because strain elastography would not be affected by the pressure exerted on the cervix. Furthermore, although strain elastography is good for measuring stiffness differences, such as stiff tumour inside softer liver tissue, it is not designed to measure overall variations in stiffness, as in cervical consistency. [31]

The aim of this study is to assess the cervical consistency by shear wave elastography in prediction of preterm birth in multiple pregnancies.

#### *Hypothesis:*

We hypothesize that a ‘soft’ cervix as indicated by shear wave elastography is positively associated with the risk of preterm birth in twin pregnancies.

#### **Design of study**

This is a prospective non-interventional observational study.

#### **Methods**

Chinese women carrying multiple pregnancies attending antenatal visit at Prince of Wales Hospital are invited to join the study. The study details will be explained by the research assistant or one of the investigators and informed consent will be obtained. Demographic data, antenatal history will be obtained. Exclusion criteria include an age of less than 18 years, non-Chinese, inability to provide consent and those who refuse to join.

Other risk factors of preterm delivery will also be documented:

- known cervical insufficiency
- surgical cerclage or pessary in previous pregnancy
- history of preterm prelabour rupture of membranes (PPROM) or spontaneous preterm birth before 34 weeks
- history of cervical surgery including cone biopsy, loop electrosurgical excision procedure, cervical tear repair, etc

- short cervix <2.5cm cervical length
- painless cervical os dilatation

A trained researcher or an obstetrician will perform transvaginal scan for the cervix on the same day of the antenatal visit, or on a separate study date, if necessary. Measurements will be done at 5 visits: 11-15 weeks, 16-19 weeks, 20-23 weeks, 24-27 weeks, 28-32 weeks. The number of visits will be depended on when the subjects are initially recruited.

The following will be measured:

- Cervical consistency by sonoelastography
- Cervical length by 2D ultrasonography
- Posterior cervical angle by 2D ultrasonography
- Fetal viability

The TVS measurement of the cervical length, posterior angle and sonoelastography is elaborated as follow:

- An USG machine equipped with shear wave elastography (SWE) is used (scale set to 0-100kPa)
- Participants are asked to empty the urinary bladder before TVS, and lie in lithotomy position
- A 12-3MHz transvaginal transducer (with double condom cover and lubricant) is inserted into the vagina gently, with no pressure exerted on the cervix
- The mid-sagittal view of the cervix is obtained and magnified
- The cervical length and the posterior angle are then measured as described in our previous study [32, 33]
- SWE mode is then switched on and a color box showing the elastogram is demonstrated
- The color box will be placed at the central part of the anterior lip of the cervix (more proximal to the USG probe than the posterior lip)
- Once the color box is uniformly filled with color signals on the elastogram, the image is frozen and a region of interest (Q-box) of size 10mm is placed to measure the tissue elasticity (in term of kPa).
- Women will be asked to perform Valsalva maneuvers and measurements of cervical

length, posterior angle and elastography will be obtained under such maneuver.

- The acquisition time is kept short within ten seconds to avoid erroneous data collection.
- Images will be saved for future analyses, if necessary.

Women, including those who are found to have a short cervix, will be managed according to the departmental protocol and their obstetric management will not be affected by the study. The obstetrician will be blinded to the finding of the sonoelastography and the finding would not affect the obstetric management of the women.

The delivery data and neonatal outcome will be collected from the medical notes and hospital electronic system before the women are discharged after their delivery.

#### **Main outcome measures:**

1. The association of cervical consistency in mid trimester with spontaneous preterm birth in women carrying multiple pregnancies.
2. The change in cervical consistency during pregnancy in women carrying multiple pregnancies.

#### **Sample Size:**

The risk of preterm birth <34 weeks in twin pregnancies is approximately 20%. A sample size of 120 was determined as being sufficient to test the diagnostic performance of cervical elasticity in mid trimester assuming that the risk of preterm delivery <34 weeks vs >34 weeks is 1:5 and that cervical elasticity area under curve (AUC) of the receiver operating characteristics (ROC) curve was 0.7, with 80% power and alpha of 5%. From the start of recruitment up to March 2018, only 15 (34.1%) out of 44 cases had completed all five serial cervix measurements. We aim to collect 120 completed set of measurements to allow our result to be statistically significant. Therefore, we increase the sample size to 200.

#### **Statistical Analysis:**

Changes in the cervical elastography will be compared using the Student paired two-tailed t test, and in the case of unequal standard deviation (SD), using a Wilcoxon signed-rank paired

two-tailed test. For comparison of frequencies, Chi-square test, or a two-sided Fisher exact test will be used where appropriate. Linear regression will be used to assess the correlations. Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 20.0 (SPSS, IL). The level of statistical significance is set at  $p < 0.05$  (two-sided).

### **Purpose and Potential**

A significant improvement in the prediction of preterm delivery allows accurate differentiation of those women who would benefit from treatment for prevention of preterm birth in multiple pregnancy. This would avoid unnecessary intervention, reduce maternal and fetal complications, and has a potential to save medical cost.

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