School of Molecular and Life Sciences

Can Shear Wave Elastography be of Value in the Assessment of Cervical Strength for the Prediction of Preterm Birth?

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This thesis is presented for the Degree of
Doctor of Philosophy
of
Curtin University

April 2020

Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), approval number HRE2016-0128.

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April 2020

Abstract

Preterm birth has far reaching ramifications and long term health consequences. There are numerous medical and environmental factors that increase the risk of preterm birth, but one of the strongest indicators to date is a shortened cervical length as identified by transvaginal ultrasound. Even so, many women with a short cervix will still deliver at term and many preterm deliveries occur in women who present with a normal length. The main aim of this research was to determine if it is possible to identify reduced cervical strength using two dimensional shear wave elastography, with greater sensitivity than cervical length.

The methodology for this research encompassed firstly gaining an understanding of shear wave technology and its application in biological tissues. Following on from this was technique development for the use of two dimensional shear wave on the cervix with a transvaginal ultrasound approach, performed on low risk non-gravid women. A technique for using a transabdominal ultrasound approach was then developed on gravid participants following experimentation with ultrasound phantoms. A comparison between shear wave speeds obtained in the transabdominal and transvaginal ultrasound approaches was then performed. Finally, the main aim of this study was to assess the shear wave speeds obtained for participants who underwent the transabdominal technique, and correlate these speeds to the time until birth of the fetus following the ultrasound scan. All participants were required to give informed consent to the extra imaging and to be contactable following the birth of the fetus for the gravid participants. In the gravid participants the consent was two tiered, patients could consent to either both the

transvaginal and transabdominal ultrasound approaches, or the transabdominal approach alone. Consent could be withdrawn at any time.

The results of this study include the following.

- The identification of the fact that reliability indicators supplied as part of the shear wave technology and the standard deviation value are important indicators for the sonographer to decide if the movement of the shear wave through the region of interest has been reliable

Results for the technical development of the transvaginal ultrasound approach:

- The number of reliable shear wave values obtained from 69 participants at the anterior and posterior portions of the external and internal os were 63, 55, 55 and 26 respectively
- The mean speed obtained at the anterior and posterior portions of the external os were 2.52 ± 0.49m/s and 2.87 ± 0.63m/s respectively
- The mean speed obtained at the anterior and posterior portions of the internal os were 3.29 ± 0.79m/s and 4.10 ± 1.11m/s respectively
- Shear wave speed measurements obtained with increased transducer pressure against the cervix were 4.89 ± 1.79m/s and 5.13 ± 1.91m/s at the anterior and posterior portions of the external os respectively
- Shear wave speed measurements obtained with reduced transducer pressure against the cervix were 2.42 ± 0.52m/s and 2.64 ± 0.57m/s at the anterior and posterior portions of the external os respectively

- Shear wave speed measurements obtained with increased transducer pressure against the cervix were 5.23 ± 2.04 m/s and 5.26 ± 0.65m/s at the anterior and posterior portions of the internal os respectively
- Shear wave speed measurements obtained with reduced transducer pressure against the cervix were 3.36 ± 0.51m/s and 4.62 ± 1.18m/s at the anterior and posterior portions of the internal os respectively

Results for the technical development of the transabdominal ultrasound approach for obtaining shear wave speed measurements on the maternal cervix.

- The mean shear wave speed obtained with the transducer in direct contact with the quality assurance phantom was 1.94 ± 0.04m/s, and through the saline-filled standoff was 1.96m/s ± 0.01m/s
- For 50 participants the number of reliable shear wave speed measurements obtained at the anterior and posterior portions of the external os were 49 and 38 respectively, and for the anterior and posterior portions of the internal os 47 and 42 respectively
- The mean shear wave speed obtained at the anterior and posterior portions of the external os was 2.01 ± 0.51m/s and 2.38 ± 0.47m/s respectively
- The mean shear wave speed obtained at the anterior and posterior portions of the internal os was 2.49 ± 0.50m/s and 2.58 ± 0.41m/s respectively

Both the transvaginal and transabdominal ultrasound techniques were used on 37 of the gravid participants. The shear wave speeds obtained with each approach were compared for differences. The differences found between each ultrasound approach in the four regions of the cervix were as follows. The differences between the transvaginal and transabdominal approach were statistically significant at the anterior portion of the internal os at 0.67m/s (SE 0.15);$t_{(26)} =$ 4.43, (*p*=0.00), and at the posterior portion of the internal os being 0.52m/s (SE 0.14);$t_{(10)} =$ 3.72, (*p*=0.04). The mean difference at the posterior portion of the external os was not statistically significant at 0.07m/s (SE 0.13);$t_{(21)} =$ -0.50, (*p*= 0.62), and also at the anterior portion of the external os 0.15m/s (SE 0.09);$t_{(34)} =$ 1.80, (*p*= 0.08)

The results of the main aim of this research investigated if it is possible to identify women who are at an increased risk of preterm delivery prior to a reduction of cervical length. This was conducted using the transabdominal technique on 455 participants. The anterior portion of the internal os showed a significant correlation between shear wave speed and the time until delivery of the fetus, R^2 Linear = 0.025 (*p*=0.001). The ratio of the internal os over the external os in the anterior cervix showed a significant correlation to time until delivery of the fetus, R^2 Linear = 0.011 (*p*=0.030). The posterior portion of the internal os showed a significant correlation between the shear wave speed and the time to birth for the spontaneous births only R^2 Linear = 0.017 (*p*=0.05). The linear correlation in all of these regions increased in significance when applied to the participants who presented between the start of the 18th week and the end of the 20th week of pregnancy for their ultrasound examination who went into spontaneous labour. The anterior and posterior portions of the external os showed a non-significant correlation between shear wave speed and time to delivery for all patient groups (*p*>0.05).

In conclusion, this work has found that a localised pre-stress can cause artifactual elevation of the shear wave speed in the transvaginal ultrasound approach and transducer pressure should be kept to a minimum. The anterior portion of the cervix is more likely to produce reliable shear wave speeds than the posterior portion in both transabdominal and transvaginal ultrasound approaches. In both ultrasound approaches the internal os produces shear wave speeds that are faster than in the external os. In both ultrasound approaches the posterior portion of the cervix produces shear wave speeds that are faster than the anterior portion. The transvaginal ultrasound approach produces faster shear wave speeds overall than the transabdominal approach, with these differences being greatest at the internal os. Using a non-invasive transabdominal ultrasound approach, this research has shown that it may be possible to identify women who are at increased risk of preterm birth who exhibit a reduction in shear wave speeds at the anterior portion of the internal os, and a reduction in this speed compared to the external os.

Acknowledgements

First and foremost I would like to express my gratitude and indebtedness to my supervisors Professor Zhonghua Sun and Ms Marilyn Zelesco.

It is hard to express how much I appreciate Zhonghua for his unending support throughout this project, his amazingly quick response to my emails and the many hours of proof reading and suggestions. No question was too small or big, and his willingness to give his advice from his wealth of knowledge is endless.

To Marilyn for her clinical expertise and support of this project, I am so appreciative of all of the time that you have put into helping me and mentoring me throughout this project. Your advice and suggestions have been invaluable and I am forever grateful for the hours that we have spent investigating shear waves.

I would also acknowledge all of the assistance from Mr Gil Stevenson for the statistical analysis used in this project. Gil has given timeless support and has educated me extensively in the application of statistical analysis for this research. He has also challenged me to improve my understanding of statistical analysis and how to apply it in this project, and I will be forever appreciative of his support.

I am humbled and overwhelmed by the support of my fellow Sonographers at SKG Radiology. Most importantly I could not have gotten through this project without the support of Tasha Warwicker and Karen Rocke. I don't know how to thank you both enough for helping me so much in this endeavour. I am also grateful to the Management team and Clinical Standards Committee at SKG Radiology for their support of this project, and the team at Canon Medical Systems Australia and Japan. I am appreciative of the support of the team at Canon Medical Systems in getting this project up and running and I am very appreciative of the time given, and the many emails between myself and the team in Japan answering all of my many questions about shear wave technology.

There are many other Sonographers and ultrasound students that assisted in this project in differing facets of the data collection, and some of the more tedious tasks involved in research, and for this I am also very grateful. The list of people to thank is as follows:

Aimee Moffat
Allana Slater
Alyce Mostert
Anita Fraser
Chandelle Hernaman
Donna Coleman
Frances Doubell
Firdos Malik
Githana Sularko
Graham Plint
Haylee Sholer
Jason Austin
Jonessa Wereley
Juliette Illif
Katrina Lonsdale
Lyn Ong
Lynn Taylor
Michelle Lim
Mukesh Lala
Pascale Brockman
Rebecca Flunder
Rojeen Amani
Shaun Bishop
Stephanie White
Steve Abbott

Last but not least I would like to thank my family and friends for their unending support. To my husband Brett and children Michael, Patrick and Crystal. Thank you for your support of this project and your encouragement in this work to try to help women, and reduce the rates of preterm birth. Thank you also to my wider family for their support and encouragement.

List of publications included as part of the thesis

- O'Hara, S., M., Zelesco, K., Rocke, G., Stevenson, and Z. Sun. 2019c 'Reliability Indicators for 2-Dimensional Shear Wave Elastography', *J Ultrasound Med*, 38: 3065-3071.

- O'Hara, S., M. Zelesco, and Z. Sun. 2019b 'Shear Wave Elastography on the Uterine Cervix: Technical Development for the Transvaginal Approach', *J Ultrasound Med*, 38: 1049-60.

- O'Hara, S., M., Zelesco, and Z. Sun. 2019a 'Shear wave elastography of the maternal cervix: A transabdominal technique', *Australasian J Ultrasound Med*. 22(2):96-103.

Publications under review

- O'Hara, S., M. Zelesco, and Z. Sun. Shear wave elastography of the maternal cervix: A comparison of transvaginal and transabdominal ultrasound approaches, *J Ultrasound Med*

- O'Hara, S., M. Zelesco, and Z. Sun. Assessment of Shear wave elastography of the maternal cervix using a transabdominal ultrasound approach for the prediction of preterm birth

Statements of contributions of others

Sandra O'Hara input into this study and the associated papers as well as the dominant contribution to the intellectual property involved in the project. As is almost always the case in conducting research studies with assistance by collaborators, other researchers made contributions to the work that were significant enough to warrant co-authorship on the resulting journal articles.

Sandra O'Hara Professor Zhonghua Sun

This study has been registered with the Australian New Zealand Clinical Trials Registry: ACTRN12616000934448

List of conference presentations

National Conference for the Australasian Sonographers Association - Brisbane, Australia, May 2019

- Cervix shear wave elastography – A comparison of transvaginal and transabdominal techniques

Internal Conference for the World Federation of Ultrasound in Medicine - Melbourne, Australia, September 2019

- Cervix shear wave elastography - Pitfalls for the transvaginal technique
- Can shear wave elastography of the maternal cervix be of use for the prediction of Preterm birth? - Preliminary results

Inaugural Curtin University MLS HDR Science Symposium - Perth, Australia, December 2019

- Can shear wave elastography of the cervix be of use in predicting imminent cervical insufficiency and preterm birth? Preliminary results

National Conference for the Australasian Sonographers Association – Melbourne, Australia, October 2020

- Can shear wave elastography be useful for the prediction of preterm birth? (abstract accepted)

National Conference for Sonic Medical Imaging – Queensland, Australia, March 2021

- Can shear wave elastography be useful for the prediction of preterm birth? (invited)

Awards

National Conference for the Australasian Sonographers Association - Brisbane, Australia, May 2019

- Best research oral presentation
- Best presentation overall

Introduction to Thesis

This project was born from an interest in the role of the Sonographer in determining how the cervix should be imaged during pregnancy, to predict the likelihood of preterm birth. A Masters project was initially conceived to assess the accuracy of different ultrasound approaches that can be used to obtain the length of the maternal cervix. The length gives the clinician an indication of the strength of the cervix, with a shorter length raising the suspicion of cervical insufficiency and increasing the likelihood of spontaneous preterm birth. The cervix is a collagenous and muscular organ, and the advent of shear wave elastography on commercial ultrasound systems led me to consider the possibility of this technique as a tool for assessing the strength of the cervix, to possibly give more information than the length of the cervix alone. Thus I embarked on this journey to see if this could be the case, with the hope of improving patient outcomes by identifying patients that should be treated for imminent cervical insufficiency with greater sensitivity than assessment of cervical length.

This project investigated the use of two dimensional shear wave elastography on biological tissues and the maternal cervix. Shear wave elastography is affected by a number of ultrasound artifacts and the effect of these artifacts on the reliability of the shear wave speeds being produced has been investigated and is discussed in chapter 2. The use of shear wave elastography on the cervix and development of the transvaginal technique was conducted using a low risk population of non-gravid patients. The development of the technique and pitfalls that can be encountered and reliability of this technique has been discussed in chapter 3. Chapter 4 discusses the use of two dimensional shear wave elastography (2D SWE) using a transabdominal ultrasound technique that was developed during this research and applied to the cervix in gravid patients. Chapter 5 discusses a comparison of the transabdominal and transvaginal ultrasound techniques for obtaining shear wave speeds in the maternal cervix. The main goal of this project was to investigate if by obtaining shear wave speeds on the maternal cervix using 2D SWE, if it is possible to predict which patients are at risk of developing cervical insufficiency and imminent preterm birth with greater sensitivity than cervical length. These results are discussed in chapter 6.

Thesis Outline

This thesis is composed of seven chapters. Chapter 1 is the background for this research. It is inclusive of a discussion on the mechanisms of preterm birth, and a literature review discussing the cervix and its role in preterm birth, and the current role of ultrasound. The final part of this chapter is a review of the current literature into the use of shear wave elastography on the cervix. Chapter 2 is the chronologically third publication for this project and discusses reliability indicators for 2D shear wave elastography. Chapter 3 is the chronologically first publication and is titled Shear wave elastography on the uterine cervix: Technical development for the transvaginal approach. Chapter 4 is Shear wave elastography of the maternal cervix: A transabdominal technique. Chapter 5 is “Shear wave elastography of the maternal cervix - comparison of transabdominal and transvaginal ultrasound approaches”, the article for this chapter is currently under review with the Journal of Ultrasound in Medicine. Chapter 6 is “Can shear wave elastography of the maternal cervix identify patients at risk of preterm birth with greater sensitivity than cervical length?”. The article for this chapter is being prepared for submission to a peer reviewed medical journal.

Finally Chapter 7 is a summary of conclusions from this research and the future directions that could be taken with the work that has been discussed in this thesis.

Statistical analysis

To assess the agreement of variables obtained in this research, t-tests have been used in chapters 2, 4 and 5. The difference between the variables has been firstly tested for normality. This has been performed due to non-normal data being problematic for this type of testing.[1,2] The significance level of all testing was p=0.05. Bland-Altman plots have been used to demonstrate the outcome of the t-tests in chapter 5. These plots demonstrate the line of zero measurement bias, the line of bias between measurements and the 95th confidence intervals have been formulated and demonstrated in the Bland-Altman plots.[3]

Nonparametric testing of normality of the difference between the variables was performed using the one-sided Kolmogorov-Smirnov test with Lilliefors correction[3] and a significance level of p=0.05. This non-parametric testing method that is suitable for continuous variables and no assumption about the shape of the distribution is required. This test is based on assessment of the maximum difference between the observed and expected cumulative-normal distribution.[4] The Lilliefors corrects the significance value of the sample mean and standard deviation in place of a hypothesized population mean and SD.[5] The Kolmogorov-Smirnov test is also suitable for large numbers of data and it is suitable to test a data set with repetitive values in the data set.[4]

Linear regression analysis was performed in chapter 6 to correlate the shear wave speed obtained with the time until birth following the examination, with a level of statistical significance of *p*=0.05. An R value of 1 indicates that the data is a perfect fit for the linear model. R values of less than 1 indicate there is some variability in the data that cannot be accounted for, and an R value of 0.5 indicates that 50% of the variability in the data cannot be explained by the model.[6,7] The low number of early preterm births in the data set limited the usefulness of other testing methods.

Testing of agreement of measurements obtained between sonographers was performed using the intra-class correlation co-efficient (ICC). ICC estimates and their 95% confidence intervals were calculated based on a mean rating absolute agreement, 2-way mixed effects model. The ICC defines poor agreement as being a value close to 0 and a high level defined as 1.[8] This method has become the accepted method of testing agreement of measurements obtained between operators in medical health publications.[9,10]

Data analysis for this research was performed using SPSS version 26.0 (SPSS V26.0, Chicago, USA).

References

1. Kim TK, Park JH. More about the basic assumptions of t-test: normality and sample size. Korean journal of anesthesiology. 2019; 72(4):331-335.

2. Rochon J, Gondan M, Kieser M. To test or not to test: Preliminary assessment of normality when comparing two independent samples. BMC Medical Research Methodology. 2012; 12(1):81.

3. Bland JM, Altman DG. "Statistical methods for assessing agreement between two methods of clinical measurement." The Lancet. 1986 Feb 8;1(8476):307-310

4. Yazici B, Yolacan S. A comparison of various tests of normality. Journal of Statistical Computation and Simulation. 2007; 77(2):175-183.

5. Lilliefors HW. On the Kolmogorov-Smirnov Test for Normality with Mean and Variance Unknown. Journal of the American Statistical Association. 1967; 62(318):399-402.

6. Lane DM. Oline statistics book, Regression analysis, Interential statistics for b and r. Chapter 14 (cited 2020 June 5th). http://onlinestatbook.com/2/regression/intro.html

7. Hamilton DF, Ghert M, Simpson AHRW. Interpreting regression models in clinical outcome studies. Bone & joint research. 2015; 4(9):152-153.

8. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. Journal of chiropractic medicine. 2016; 15(2):155-163.

9. Fleiss JL, Cohen J. The Equivalence of Weighted Kappa and the Intraclass Correlation Coefficient as Measures of Reliability. Educational and Psychological Measurement. 1973; 33(3):613-619.

10. Rankin G, Stokes M. Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. Clinical Rehabilitation. 1998; 12(3):187-199.

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Abbreviations

ARFI – acoustic radiation force impulse

2D SWE (or 2DSWE) – two dimensional shear wave elastography

BMI – body mass index

B-mode – brightness mode

C-section – caesarean section birth

cm – centimetres

dB - decibel

EFSUMB – European federation for the society of ultrasound in medicine and biology

ICC – intraclass correlation coefficient

kPa - kilopascals

LLETZ – lower loop excision of transitional zone

MHz - megahertz

mm – millimetre

m/s – metres per second

nm – nanometre

PROM – premature rupture of membranes

pSWE – point shear wave elastography

PTB – preterm birth

ROI – region of interest

SD – standard deviation

SE – standard error

SPTB – spontaneous preterm birth

SSI – supersonic shear imaging

SWE – shear wave elastography

SWS – shear wave speed

TA – transabdominal

TV - transvaginal

TVU – transvaginal ultrasound

µm – micrometre

∞ - infinity

% - percentage

Definitions

Amniotic sac – membranous sac contain fetal parts and amniotic fluid in pregnancy

Cervical cerclage – surgical stich placed in or around the cervix to mechanically maintain the pregnancy when cervical length is reduced to 10mm or less, or in women at high risk of preterm birth

Cervical pessary – silicone device used to mechanically inhibit dilatation of the cervix

Doppler ultrasound – ultrasound technique using Doppler technology to measure the movement of blood flow in arteries and veins

Ewe – female sheep

Gravid – pregnancy

Non-gravid – not pregnant

In- vivo – taking place within the living organism

Labour - the process of delivering a baby and the placenta, membranes, and umbilical cord from the uterus to the vagina to the outside world

Nulliparous – no children

Multiparous – more than one child

Progesterone pessary – therapeutic treatment of the cervix with progesterone to increase or maintain the strength of the cervix in pregnancy

Ripening of the cervix – preparation of the cervix for labour

First trimester – week 1 to week 13 of pregnancy

Second trimester – from week 13 to week 27 of pregnancy

Third trimester – from week 27 of pregnancy to term

Shear waves – naturally occurring phenomenon that occur in the human body created during talking and breathing

Elastography – ultrasound technique that assesses elastic properties of tissues

Shear wave elastography – ultrasound technology that uses a B-mode pulsed modified into an acoustic radiation force impulse to create minute movements in tissues and produce shear waves in the region of interest, the speed of movement of the shear waves indicates the stiffness of the tissues

Preterm birth – Delivery of the fetus prior to 37 weeks of pregnancy

Extreme preterm birth – delivery of the fetus prior to 28 weeks pregnancy

Very preterm birth – delivery of fetus between 28 and 32 weeks of pregnancy

Moderate to late preterm birth – delivery of the fetus between 32 and 37 weeks of pregnancy

LLETZ procedure – excision of tissues of the cervix following the finding of abnormal cells

Fibroidectomy – surgical removal of fibroids from the uterus

Mullerian abnormalities – congenital malformation of the mullerian duct during embryogenesis resulting in congenital malformation of

Figures and Figure Legends

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Chapter 1

Literature Review

1.1 Background – Preterm Birth

The definition of preterm birth (PTB) is delivery of the fetus before the 37th week of pregnancy. This can be further categorised into early preterm birth occurring before 34 weeks gestation, very preterm between and 28 and 32 weeks gestation and extremely preterm prior to 28 weeks of pregnancy.[1] In 2016 the Australian Institute of Health and Welfare reported an overall PTB rate of 8.6%, this is an increase from 2011 when PTB occurred in 7.5% of all gestations.[2] Most (81.1%) of PTB's occurred between 32 and 36 weeks of gestation, with the average age for all preterm births being 33.4 weeks. Preterm birth is linked to increased perinatal mortality and morbidity. For all live births during the period to 2016, the average gestation at birth was 38.7 weeks of pregnancy. The average gestation at which a stillbirth occurred was 26.6 weeks gestation. Overall, 85.8% of stillborn babies occurred with a preterm birth, with the remaining occurring in term pregnancies.[3]

The risk of PTB has been shown to be increased by numerous environmental and medical factors. These risks are as follows:

- Lower socio economic status
- Lower levels of maternal education
- Single marital status
- Increased alcohol consumption
- Smoking during pregnancy, increasing if >10 cigarettes per day
- Illicit drug use
- Physical abuse
- Stress
- Remote geographical location

- Inadequate prenatal care
- Low pre-pregnancy weight
- Poor weight gain in pregnancy
- Short interval between pregnancies
- Previous preterm birth
- Assisted reproductive technology
- Pre-existing or gestational diabetes
- Urogenital infections during pregnancy, for example chlamydia or bacterial vaginosis
- Uterine anomalies
- Excisional cervical treatment for cervical intraepithelial neoplasia
- Previous fibroidectomy
- Antepartum bleeding
- Multiple gestation
- Fetal anomaly
- Polyhydramnios
- Cervical insufficiency [4]

Some authors have also shown an association with PTB as follows:

- Ethnicity – increased risk of very preterm birth among East African immigrants and African American women
- Increased body mass index (BMI) – obesity or more than the recommended pregnancy weight gain
- Emotional health and wellbeing – PTB is more likely in socially unsupported patients, untreated depression and anxiety [4]

Factors that lead to PTB during pregnancy are as follows:

- Delivery for maternal or fetal indications, in which labour is either induced or the infant is delivered by pre-labour caesarean section
- Spontaneous preterm labour with intact membranes
- Preterm or premature rupture of membranes (PROM), irrespective of whether delivery is vaginal or by caesarean section [4]

Preterm birth is considered the leading cause of perinatal mortality or morbidity that is not attributed to other factors such as congenital abnormalities or aneuploidy.[5] It is associated with neurological disability, inclusive of but not limited to cerebral palsy, abnormal vision, mental retardation and an increased risk of chronic lung disease.[5, 6] Behavioural problems and lower achievement in education and an increase in the incidence of PTB in the second generation have been documented into adulthood.[5] The impact of PTB on society and the individual at the time of birth, and into the future, makes recognition of patients at increased risk of PTB an important goal to help aid in an overall reduction in PTB rates in not only Australia, but also globally.

Even though numerous factors that increase the risk of PTB have been identified as described, many women who deliver preterm have no known risk factors [7, 8]. Out of the risk factors mentioned above, the strongest correlation to spontaneous preterm birth (SPTB) is a history of prior preterm birth(s). Women who have had a prior SPTB have a 2.5-fold increase in risk of SPTB occurring in a subsequent pregnancy. In nulliparous patients who present with no prior gestational history this risk factor is not useful, and nearly 50% of patients who experience SPTB are in their first pregnancy.[9] Whilst in women who have had a term birth/s in a previous pregnancy or pregnancies, the risk of SPTB occurring in subsequent pregnancies is decreased.[10]

A shortened cervical length that is identified using transvaginal ultrasound (TVU), increases the risk of a SPTB occurring in the pregnancy to a significant level.[11] In cases where a patient presents with a medical history that also increases their risk of SPTB, if TVU finds that the cervical length is reduced, there is a greater than 50% sensitivity of SPTB occurring in the pregnancy. However, in the unselected population the sensitivity of a shortened cervical length identified on TVU is reduced to only 37%,[12, 13] This reduced sensitivity, particularly in low risk women, warrants the need for a screening tool that will improve the sensitivity of identifying cervical insufficiency in these women.

1.2 **The Cervix**

The cervix extends from the junction of the lower uterine segment and endocervix to the junction of the ectocervix and vagina. The cervical canal is continuous with the endometrial canal of the uterus superiorly and the vaginal vault inferiorly. In the non-gravid state, the length of the cervix measures approximately 25mm, and the width between and 20 to 25mm. The canal of the cervix is central and is surrounded by collagenous and smooth muscle tissue with an approximate width of 10mm.[14]

The human cervix has previously been quantified as being mostly collagenous in structure with minimal smooth muscle cellular content. Recent histological research into its structure has shown greater concentrations of smooth muscle cells than previously thought.[15] Vink et al[15] have shown that there is a layer of fibres of smooth muscle that run longitudinally along the length of the canal that wrap around the central canal. The next layer is composed of smooth muscle and collagenous cells, and this layer wraps in a circumferential direction around the layer of longitudinal smooth muscle. [15] There are different concentrations of smooth muscle cells in this circumferential layer. The highest concentration is in the internal os of the cervix and this is composed of approximately 50-60% of smooth muscle cells. The lowest concentration is in the external os, with this region having approximately 10% of smooth muscle cells with the collagen, with the middle portion of the cervix containing around 40% smooth muscle cells. [15] The fibrils of collagen in the cervix at a size of approximately 10-500nm, bundle together to form fibres of collagen to a size of approximately 1-500µm, these then bundle together in their preferred directions to form an ultrastructure of tissue that has a size of between 1-10 mm.[16] The radial outer region of the cervix contains larger blood vessels and an arteriole and venule network, and adjacent to the central canal are small veins and capillaries also.[15] The research by Vink et al[15] assessed the structure of the cervix in specimens from nulliparous patients and also multiparous patients, and concluded that the structure of the cervix had little to no difference between these specimens.

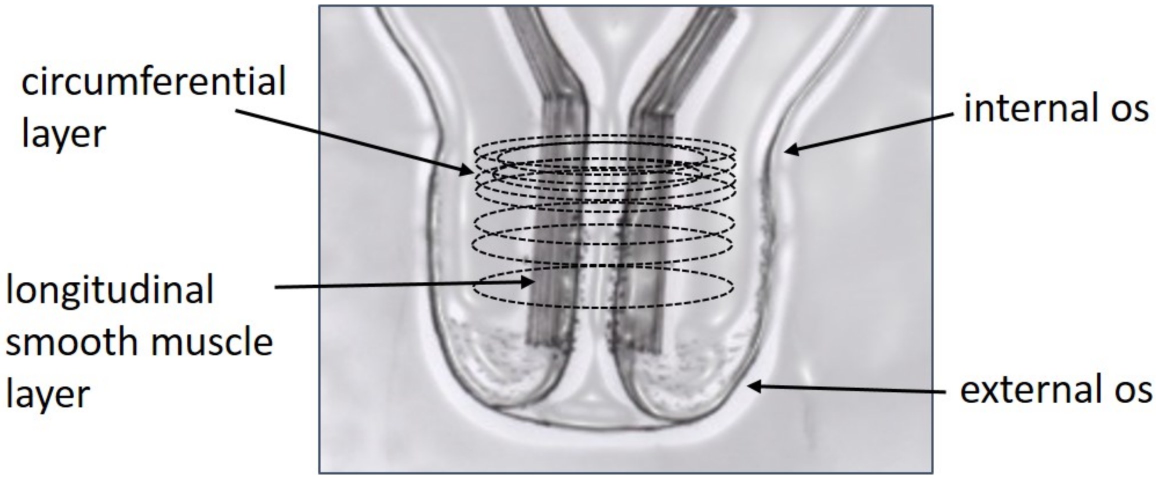


Figure 1.1: Diagram of the cervix illustrating the circumferential layer of smooth muscle and collagen in greater concentration at the internal os creating the sphincter like effect, and the longitudinal smooth muscle layer adjacent to the cervical canal.

The longitudinal and circumferential layers of the cervix are thought to be responsible for different actions during labour and birth of the fetus. The action of shortening or effacement of the cervix is thought to be due to the longitudinal fibres, whereas the action of dilatation of the cervix is thought to be due to the circumferential layer of collagen and muscle fibres, and thus this circumferential layer is also thought to be responsible for inhibiting dilatation of the cervix until the onset of labour. [14] This has led to the hypothesis that the layer of circumferential smooth muscle cells and collagen may be having a sphincter like effect due to the greater concentration of smooth muscle cells in the internal os, in the main part to retain the pregnancy in the uterus until the onset of labour.[15] Supporting this theory, it has been found previously that the internal os is tightly closed during the luteal phase of the ovarian cycle and relaxes for the onset of menstruation.[14]

The cervix has a difficult task to perform during pregnancy. The cervix must have the strength to maintain the pregnancy until the onset of labour wherein it must soften and dilate to allow delivery of the fetus. Following this, the cervix must return to its original structure and perform this task again in subsequent pregnancies.[17] During pregnancy the cervix is affected by multiple mechanical forces. The largest of these forces being the weight of the developing fetus. The amniotic sac will also apply tension to the cervical canal and in some cases this tension will be increased by adherence of the amniotic membrane to the internal os. The muscles of the pelvic floor may also be responsible for part of the force placed on the cervix over the duration of pregnancy.[16] The strength of the cervix equates to its ability to maintain the pregnancy until greater than 37 weeks of gestation. For the fetus to be delivered vaginally the cervix softens, shortens and dilates to allow passage of the fetus.[18] The initial softening of the cervix can take from several days to weeks and can be quite a slow process, whilst ripening of the cervix for delivery can take several hours or up to several days.[19]

If the cervix softens before the term of the pregnancy, this can lead to cervical insufficiency and shortening of the length of the cervix, and SPTB. [16] Historically a digital examination was performed by the clinician to assess the stiffness of the cervix to assess for softening. This method of assessment was problematic due to interpretation by the individual clinician. Another problem with the digital technique is that assessment is limited to interrogation of the external os, whereas it has been shown that the cervix will soften first at the internal os and the external os will be the last region of the cervix to soften. [7, 16, 20]

The length of the cervix obtained using a TVU approach has become the standard method for assessing the strength of the cervix during pregnancy and identifying cervical insufficiency. [21] A short cervical length identified on TVU has been shown to be a strong indication of SPTB. This indication is significant in both singleton and twin pregnancies. The shorter the length of the cervix, and the earlier in the pregnancy that this shortened length is identified, the greater the risk of SPTB. [11]

1.3 Ultrasound of cervical length

Whilst the gold standard for measurement of cervical length is using TVU,[5] there are alternate ultrasound approaches that can be used. Using ultrasound, the cervix can also be measured using either a transabdominal or transperineal ultrasound approach. However, it has been recommended that the TVU approach is used for women who present with a medical history that increases their risk of preterm birth in the current pregnancy. [9, 22]

There has been some work assessing the use of the transabdominal and transperineal ultrasound approaches and comparing their accuracy to the transvaginal approach. The transperineal approach can replicate transvaginal cervical length, but problems with the use of a lower frequency transducer and overlying rectal gas have resulted in the length being unobtainable in between 10 and 20% of patients.[23, 24] The transabdominal approach has also been shown to replicate the transvaginal approach for measurement of cervical length if an empty maternal bladder is used,[7, 25] though this technique can also be problematic for adequate visualisation of the cervix. A number of authors have shown that they are able to measure the cervix in 80 to 100% of cases using this technique.[26-29] The cervical length can also be measured using a transabdominal approach with a full maternal bladder. This technique allows visualisation of the cervix in 100% of cases,[5, 26] but the overly distended maternal bladder has been shown to cause an artifactual lengthening of the cervix compared to the transvaginal approach.[26, 30] It can also be problematic in that the compression of the cervix from the full bladder can mask a premature bulging of the fetal membranes.[5] The cervical length is obtainable in 100% of patients using the transvaginal approach.[26, 30, 31] This approach has the advantage of being familiar to sonographers who perform gynaecological studies, but care needs to be taken to avoid compression of the cervix that can result in an artifactual lengthening.[24, 32]

As discussed, the possibility of shortening of the cervix during pregnancy is increased if there is a history of SPTB in a previous pregnancy.[9] Other factors significantly elevating the risk of developing a short cervix in the mid-trimester of pregnancy are a previous lower loop excision of the transitional zone (LLETZ procedure), fibroidectomy, multiple dilatation and curettage procedures, and also mullerian abnormalities of the uterus.[12, 13, 33] There is also a likelihood that shortening of cervical length can be caused by an inflammatory or infectious process.[34] Membranous separation and sludge seen within the amniotic fluid on ultrasound, in the presence of a shortened TVU cervical length, is predictive of a higher incidence of PTB than a shortened cervical length alone.[35]

The bulk of the amniotic sac and fluid, and fetal parts, and the force that it may exert on the cervix has most relevance following the 16th week of pregnancy.[7, 36] Even in patients who are at an elevated risk of PTB, the cervix is usually able to maintain strength until the 16th week of pregnancy. For this reason the use of cervical length measurements to assess cervical strength is recommended from the 16th week of pregnancy,[37] with measurement of cervical length found to be ineffective in the first trimester for the preceding reasons.[13, 35, 36] Following the 28th week of pregnancy, the relevance of cervical length for the prediction of preterm birth is reduced, this is mainly due to the unavailability of treatment following this time.[7, 37]

The larger the reduction in the length of the cervix, the greater the chance of the fetus being delivered early, and the earlier this reduced length is diagnosed the greater the chance also.[11, 33, 35, 37] At 20 weeks of gestation the median cervical length is 42mm.[38] In high risk women with a cervical length of 25mm the risk of preterm birth is 26%, this increases to 32% at a length of 20mm, and there is a 64% chance of a fetus being delivered preterm with a transvaginal cervix length of 0mm.[22, 39, 40] Currently ultrasound of a shortened cervical length is the best clinical indicator of cervical insufficiency. The low sensitivity of this technique, particularly in low risk women, means that many babies will still be delivered at term when a reduced cervical length has been found in the mid-trimester. There will also be many women who have a normal cervical length in the mid-trimester who develop cervical insufficiency and deliver preterm.[13]

In Perth, Western Australia in 2014, the Western Australian Preterm Birth Initiative embarked on a program to increase the identification of patients at risk of SPTB due to a shortened cervical length.[37] This program recommends, as per standard management paradigms, that all women who present with an increased risk of SPTB due to prior gestational history or a significantly increased risk of PTB, that transvaginal cervical length measurement is performed commencing in the 16th week of pregnancy. In women in the low risk population, a transabdominal technique with a partially full maternal bladder can be used initially. If the transabdominal cervical length is greater than 35mm then no further imaging is required, and if less than 35mm a transvaginal cervical length should also be performed.[37] This method of screening of cervical length to identify patients who are at risk of cervical insufficiency and preterm birth has been endorsed by the Royal Australian and New Zealand College of Obstetrics and Gynaecology.[41]

1.4 **Treatment of cervical insufficiency**

Standard management paradigms have been developed to treat cervical insufficiency. At 20 weeks of pregnancy, the median cervical length is 42mm.[38] A reduction in length becomes significant when it is less than 25mm using TVU,[26, 36, 38] and different treatment methods are used dependant on the length of the cervix at the time of the scan, and previous medical history.

In women who are at a medically increased risk of recurrent SPTB, particularly previous early pregnancy loss, the placement of a cervical cerclage has been used as a preventative measure, and this has been shown to effectively reduce recurrent preterm pregnancy loss.[42] The cerclage uses sutures or surgical tape in a mechanical attempt to prevent dilatation of the cervix and subsequent PTB.[43] It has been recommended that in high risk women, history indicated cerclage placement between 12 to 14 weeks of pregnancy should be considered, with cerclage removal from the 36th week of pregnancy for delivery of the fetus.[33, 37] Surveillance of high risk women with serial TVU cervical length measurement from 16 weeks of pregnancy and vaginal progesterone treatment has also been recomended.[33, 37] In patients who present with a cervical length of less than 10mm in the mid-trimester, cervical cerclage placement has been shown to reduce the preterm birth rate, and is the recommended treatment.[37] Even so cervical cerclage has also been shown to increase the risk of infection, fever and vaginal bleeding or discharge, and the rates of caesarean section delivery are also increased in patients who have undergone cerclage placement. In twin pregnancy it has been shown that cerclage placement increases the incidence of PTB and is therefore contraindicated.[35]

The cervical pessary is a device made of silicone that has been used previously to treat urinary incontinence and genital prolapse, and has now also been used to treat cervical insufficiency.[35] This mechanical device also attempts to prevent dilatation of the cervix and subsequent PTB. This device has been shown to reduce preterm birth, but the research into its use is limited by the number of studies that have been performed. It has also been shown to reduce SPTB in twin pregnancy,[35] even so clinical protocols for the use of this device are still being developed for clinical use.[43]

In low risk patients if the TVU cervical length is between 20 to 25mm in the mid-trimester, it is recommended that the examination is repeated in 1 to 2 weeks to assess stability.[33] If the TVU cervical length is between 10 to 20mm then the use of vaginal progesterone administered daily is indicated up until the 36th or 37th week of pregnancy.[33, 37] In a large trial enrolling just over 32 000 women (both at low and increased risk of PTB) with no symptoms of cervical insufficiency, vaginal progesterone was found to reduce the rate of SPTB occurring before the 34th week of pregnancy. Out of the 465 women who were identified as having a cervical length between 10 and 20mm and agreed to participate, approximately half were given a placebo with half receiving the progesterone treatment. The preterm birth rate in the placebo group was 2.1%, with a significant reduction in SPTB in the progesterone group to 1.85%.[44] Though successful in singleton pregnancies, it has been shown to be ineffective in women carrying a multiple gestation or in women who are already in labour.[43] A recent meta-analysis into the use of vaginal progesterone in singleton pregnancies has also shown that the use of vaginal progesterone decreases preterm birth among women with a length of the cervix that is 25mm or less.[45]

1.5 Elastography

Elastography is an adjunct ultrasound technique that has been utilised for many years. Shear waves are a naturally occurring phenomenon that can occur in the human body. Shear waves are produced during breathing and talking and the vibration of the tissues induces shear waves throughout the body. [46] Ultrasound elastography gives the sonographer indications of the elasticity properties or stiffness of tissues.[46] This technique is based on the theory that soft tissues will deform differently than stiff tissues. Depending on the ultrasound technique being applied, the elastographic image will identify the different level of deformation of the tissue using either a qualitative colour coded map or a quantitative reading of shear wave speed or tissue elasticity.[18]

1.5.1 Strain elastography

To assess the stiffness of tissues with ultrasound strain elastography, the transducer is used to perform graded compression against the tissues of interest. When the mechanical stress from the transducer is applied the affected tissues will experience differing levels of deformation or 'strain'. The softer tissues experience more strain than the stiffer tissues.[46] The elastogram produces a colour coded map that is a qualitative representation of the stiffness of the tissue in the region of interest. The stiffness of the tissues is represented by assigning colours in the map to represent regions of increased and decreased stiffness, and the colour elastogram is overlaid on the B-mode ultrasound image (Figure 1.1).[46]

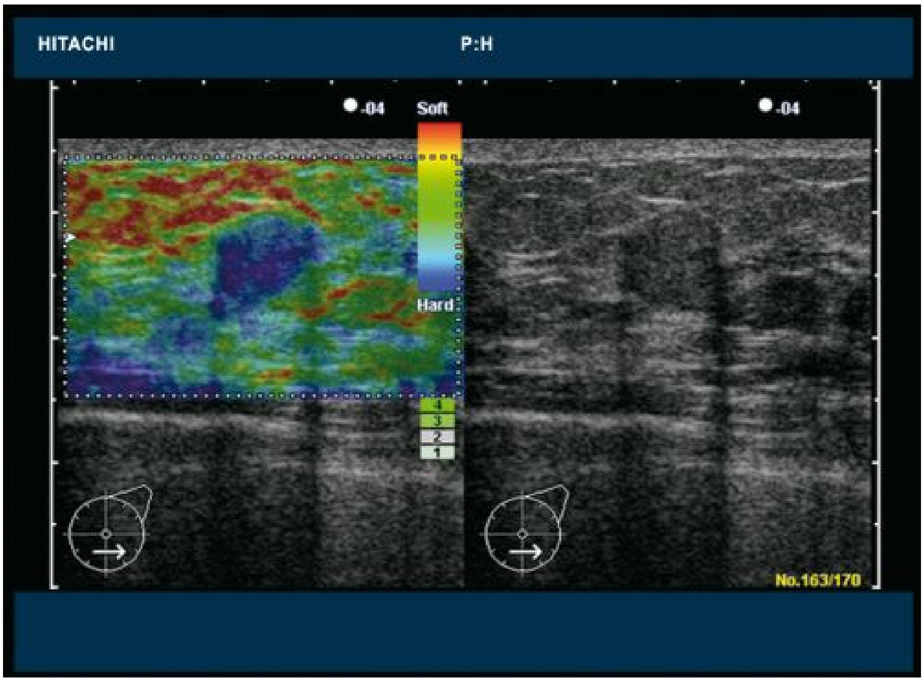


Figure 1.2: Example image showing a use of strain elastography with breast ultrasound. The red region of the map is representative of softer tissues with the blue region of the map indicative of stiffer tissue.

1.5.2 Shear wave elastography

In the late 1990's Katherine Nightingale and her team of researchers at Duke University in Durham, North Carolina, considered if it might be possible to perform 'palpation' of tissues at a remote location from the ultrasound transducer using a modified ultrasound pulse.[47] The pulse was modified to an increased intensity and a lower frequency than is used in B-mode imaging. These modified pulses are known as an acoustic radiation force impulse (ARFI). The ARFI pulse is used to excite the tissues in the region of interest to produce shear waves.[47] This technology is now used in the large part for the assessment of liver stiffness and the quantification of levels of liver fibrosis and cirrhosis.[48]

The standard B-mode ultrasound transducer is used to produce a quantifiable shear wave using the modified ultrasound pulse produced by the transducer crystals. [48] This pulse is directed vertically from the transducer face into the region of interest. This high speed acoustic pulse 'vibrates' the tissues to produce shear waves that propagate through the tissues at approximately ninety degrees to the main pulse. [48] Shear waves move at a slower velocity through the tissues and are able to be tracked by the ultrasound machine with a technique similar to Doppler ultrasonography.[48] They also move through tissue at wavelengths a thousand times shorter than sound waves of the same frequency. As the frequency of shear waves is very low, long wavelengths are produced in the region of many centimetres.[49] The main pulse will be pushed into the tissues at speeds of 10 m/s whilst the shear waves move through the tissues at much slower speeds of 1 m/s.[48]

Shear waves will move faster through stiff tissues with softer 'buttery' tissues resulting in slower shear wave propagation. By quantifying parameters related to the propagation of the shear wave, such as shear wave speed, it is expected that this technique will produce a more objective and reproducible mechanical evaluation of the cervix than strain elastography.[48,50]

Two types of shear wave elastography are commercially available; these being point shear wave elastography (pSWE) and two dimensional shear wave elastography (2D SWE). With point shear wave elastography one or two main ARFI pulses are produced and shear wave measurements are obtained within a small fixed region of interest. The region of interest is placed with the aid of a B-mode ultrasound imaging (Figure 1.2).

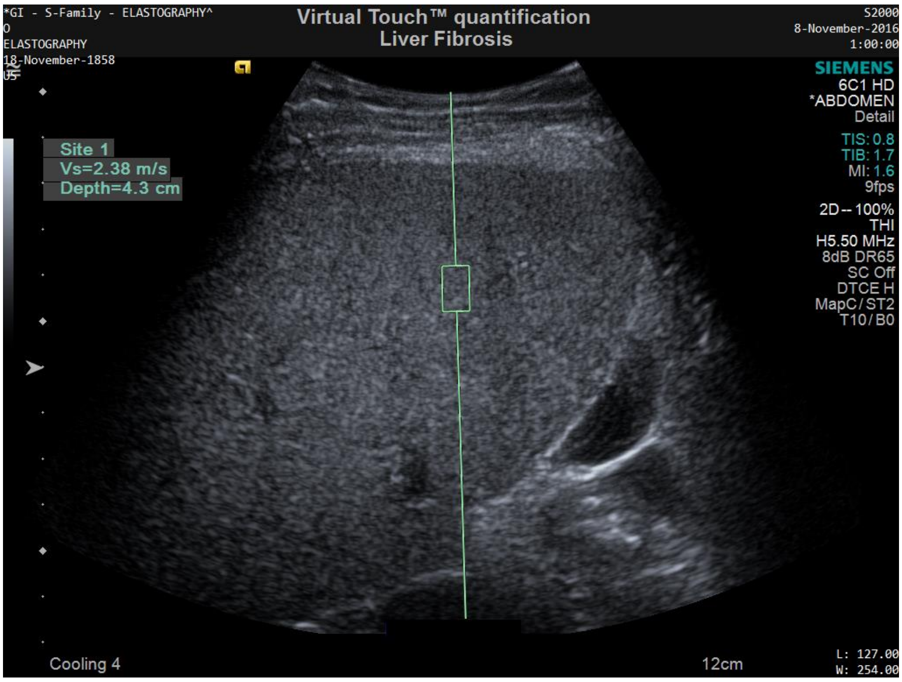


Figure 1.3: Example of pSWE being used in the liver. The shear wave speed is obtained within a small fixed region of interest.

With 2D SWE a larger region of interest can be interrogated. B-mode imaging is also used to aid the placement of the region of interest. Multiple ARFI pulses are used to produce shear waves. A larger elastogram that is flexible in size is used. In 2D SWE the elastogram also gives a colour coded qualitative representation of the speed of shear wave propagation, and ultrasound technology providers also give indications of reliable shear wave propagation over the whole region of the elastogram.[49] A smaller region of interest (ROI) is then placed within the elastogram to obtain the quantitative measurements of shear wave speed or pressure (Figure 1.3).

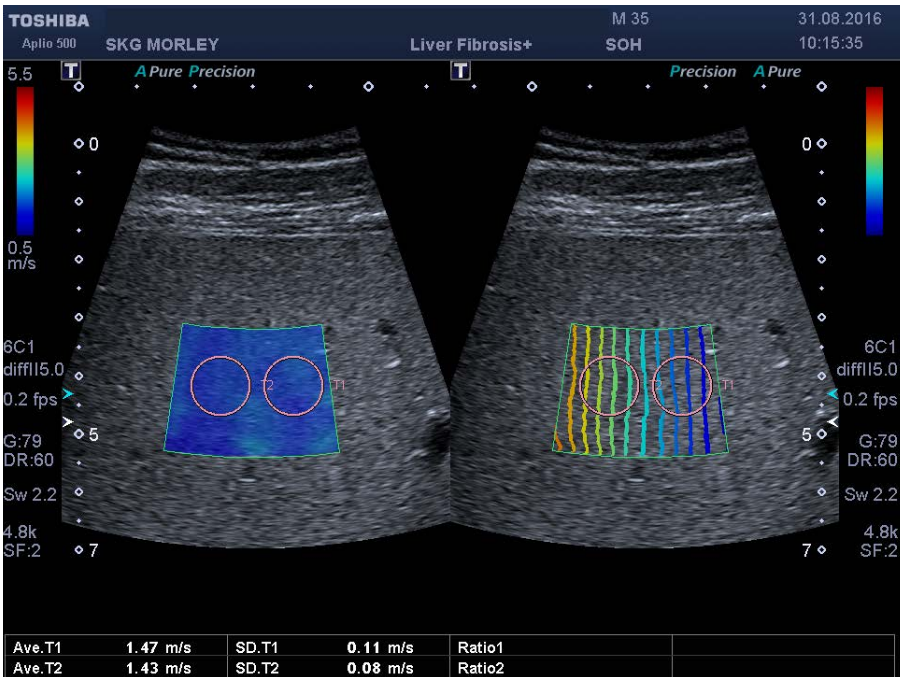


Figure 1.4: Example of the 2D SWE being used in the liver. The colour elastogram is adjustable in size and the circular ROI's can be placed within the elastogram to obtain the readings of shear wave speed.

1.6 Elastography and the cervix

1.6.1 Strain elastography and the cervix

Strain elastography has been used to make qualitative assessments of the stiffness of the cervix. The premise being that soft tissue will deform more easily than hard tissue.[48,51] A difficulty with the use of strain elastography is the lack of reference tissue around the cervix for comparison.[52,53] Whilst the main difficulty with this technique is the reproducibility of transducer pressure applied to the cervix between sonographers and the elastographic image produced can be altered by applying different levels of pressure to the cervix with the transducer.[52,53] To try and overcome this Swiatowska et al[51] and Wozniak et al[54] relied on patient breathing and arterial pulsation to create the elastographic images. Swiatowska et al[51] found that the internal os was softer in patients who underwent a successful induction of labour compared to patients with unsuccessful induction, whilst Wozniak et al[54] found that the cervix was softer in low risk women with a normal cervical length that had a subsequent preterm birth. They concluded that softening of the cervix was identifiable prior to a reduction in cervical length.[54] This study was limited by only one sonographer performing all examinations.

1.6.2 2D shear wave elastography and the cervix

There is promise for the use of 2D SWE on the maternal cervix during pregnancy to quantifiably assess cervical strength. The cervix progressively softens throughout pregnancy, and some authors have shown a reduction in shear wave speed in the cervix in the third trimester of pregnancy compared to the first trimester,[55] with some work showing a gradual reduction in stiffness as the pregnancy progresses.[19, 56]

Using a transvaginal ultrasound approach differences in shear wave speed have been observed between gravid and non-gravid patients, with the non-gravid cervix having higher shear wave speeds than in pregnany.[55] In non-gravid patients, higher shear wave speeds have also been obtained in patients with a proven malignancy compared to the normal cervix.[57] In both gravid and non-gravid patients it has also been shown that the internal os is stiffer and exhibits faster shear wave speeds than the external os,[55, 58] and the posterior portion of the cervix has been shown to be stiffer with higher shear wave speeds than the anterior portion.[56,59] Little difference in shear wave speed has been shown between nulliparous and multiparous patients.[55]

Carlson et al[59] assessed the difference in shear wave speeds obtained in hysterectomy specimens of the cervix using unripened and chemically ripened specimens, with a significant reduction in shear wave speed was shown in the ripened specimens.[59] These results were also reflected with in-vivo research on pregnant ewes, comparing a control group of four Ewes to five Ewes who went into chemically induced labour.[60] Carlson et al[61] reported on an in-vivo study of pregnant patients presenting for cervical ripening before induction of labour between 37 and 41 weeks of pregnancy. Shear wave speed measurements were obtained on ten patients prior to and following cervical ripening with a prototype linear array transducer placed intra-vaginally. A significant reduction in shear wave speeds was obtained post ripening of the cervix.[61]

Some authors have also shown a reduction in shear wave speed in the cervix in women who subsequently went into preterm labour compared to women with a full term delivery as will be discussed. It has been shown that it is feasible to examine the external os anteriorly with TVU SWE, and that a reduction in speed in this region is evident in women who deliver preterm.[62] Hernandez et al[63] have shown that a reduction in shear wave speed has a positive predictive value of subsequent preterm birth, and they have proposed a cut off value of shear wave speed below which the risk of preterm birth is increased at prior to both 37 and 34 weeks of pregnancy. The authors concluded that a softening of the cervix with a normal cervical length increased the risk of SPTB by 4.5 times.[63] A softening of the cervix combined with a reduction in cervical length increased the risk of SPTB prior to 34 weeks gestation was increased by 120 times compared to patients with a normal cervical length.[63] These conclusions are problematic due to the authors excluding the participants who delivered at term who also exhibited reduced shear wave speeds.

To date two authors have assessed the use of a transabdominal ultrasound approach to obtain shear wave speeds in the cervix to assess changes during pregnancy.[64,65] Research into the use of the transabdominal ultrasound technique on Rhesus Macaque monkeys has shown a gradual reduction in shear wave speed and stiffness of the tissues as the gestational age increases.[64] A significant difference in shear wave speeds obtained between the transvaginal and transabdominal ultrasound approaches was also shown.[64]

Agarwal et al[65] used pSWE to obtain shear wave speeds at the anterior portion of the internal os on 30 patients in the third trimester of pregnancy. Patients who delivered prior to 37 weeks of pregnancy had significantly slower shear wave speeds than those who delivered at greater than 37 weeks of pregnancy.[65] A limitation of this finding is that standard management paradigms recommend that screening of the cervix for the identification of cervical insufficiency should be performed between 16 and 28 weeks of pregnancy to facilitate the use of interventions to reduce the likelihood of subsequent SPTB.[43] Following the 28th week of pregnancy interventional techniques are of little value.[43]

1.7 **Conclusion**

There is evidence to show that a shortened cervical length is a strong indicator of cervical insufficiency and SPTB in pregnancy. The cervix is composed of muscular and collagenous fibres and a weakening of the cervix is currently identified by a reduction in transvaginal cervical length. There is potential for the use of shear wave elastography to assess the strength of the cervix and it may be possible to identify a reduction in cervical strength using shear wave elastography with greater sensitivity than cervical length.

To date, there is a limited amount of research into the use of shear wave elastography on the maternal cervix to identify patients at an increased risk of SPTB due to imminent cervical insufficiency, with most of the work using a transvaginal ultrasound approach. The current gold standard of measuring cervical length using a transvaginal ultrasound approach to assess for cervical insufficiency is only recommended in women in the high risk population. This research has developed a transabdominal ultrasound approach to acquire shear wave speeds in the maternal cervix that may be more appropriate for screening of the low risk population. To date no research has been identified that uses a transabdominal ultrasound technique in the mid-trimester of pregnancy, to investigate the use of shear wave elastography to identify a softening of the cervix prior to a reduction in cervical strength.

1.8 References

1. Honest H, Bachmann LM, Coomarasamy A, et al. Accuracy of cervical transvaginal sonography in predicting preterm birth: a systematic review. Ultrasound in Obstetrics and Gynecology. 2003; 22(3):305-322.

2. Li Z ZR, Hilder L, Sullivan EA Australia's mothers and babies 2011 Canberra: Australian Institute of Health and Welfare; 2013.

3. Australian Institute of Health and Welfare(AIHW) 2018. Australia's mothers and babies 2016—in brief . Perinatal statistics series no.34.Canberra: AIHW;

4. Department of Health 2018 Clinical Practice Guidelines; Pregnancy Care. Canberra, Government of Australia.

5. Rumack CM, Wilson , S.R., Charboneau, W.,Levine, D. Rumack C, editor. Diagnostic Ultrasound. 4th ed. Philadelphia: Elsevier Mosby; 2011.

6. World Health Organisation(WHO). Newsroom.Factsheets.Detail.Preterm Birth 2018. WHO

7. Lim K, Butt K, Crane JM. SOGC Clinical Practice Guideline. Ultrasonographic cervical length assessment in predicting preterm birth in singleton pregnancies. J Obstet Gynaecol Can [Practice Guideline]. 2011; 33(5):486-99.

8. Muglia LJ, Katz M. The Enigma of Spontaneous Preterm Birth. New England Journal of Medicine. 2010; 362(6):529-535.

9. Taylor BK. Sonographic Assessment of Cervical Length and the Risk of Preterm Birth. Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2011; 40(5):617-631.

10. Offiah I, O'Donoghue K, Kenny L. Clinical Risk Factors for Preterm Birth, Preterm Birth,- Mother and Child 2012 Available from: http://www.intechopen.com/books/preterm-birth-mother-and-child/clinical-risk-factors-for-preterm-birth.

11. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol. 2012; 206(2):124.e1-124.e19.

12. Larma JD, Iams JD. Is sonographic assessment of the cervix necessary and helpful? Clinical Obstetrics and Gynecology. 2012; 55(1):324-335.

13. Olson Chen C. Ultrasound for cervical length. Ultrasound clinics. 2013; 8(1):1-11.

14. Nott JP, Bonney EA, Pickering JD, Simpson NAB. The structure and function of the cervix during pregnancy. Translational Research in Anatomy. 2016; 2:1-7.

15. Vink JY, Qin S, Brock CO, et al. A new paradigm for the role of smooth muscle cells in the human cervix. American journal of obstetrics and gynecology. 2016; 215(4):478.e1.

16. Myers KM, Feltovich H, Mazza E, et al. The mechanical role of the cervix in pregnancy. J Biomech. 2015; 48(9):1511-23.

17. House M, Kaplan DL, Socrate S. Relationships between mechanical properties and extracellular matrix constituents of the cervical stroma during pregnancy. Semin Perinatol. 2009; 33(5):300-307.

18. House M, Socrate S. The cervix as a biomechanical structure. Ultrasound in Obstetrics and Gynecology. 2006; 28(6):745-749.

19. Ono T, Katsura D, Yamada K, et al. Use of ultrasound shear-wave elastography to evaluate change in cervical stiffness during pregnancy. J Obstet Gynaecol Res. 2017; 43(9):1405-1410.

20. Myers KM, Socrate S, Paskaleva A, House M. A study of the anisotropy and tension/compression behavior of human cervical tissue. J Biomech Eng. 2010; 132(2):021003 .

21. Retzke JD, Sonek JD, Lehmann J, Yazdi B, Kagan KO. Comparison of three methods of cervical measurement in the first trimester: Single-line, two-line, and tracing. Prenatal Diagnosis. 2013; 33(3):262-268.

22. To MS, Skentou CA, Royston P, Yu CKH, Nicolaides KH. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of

cervical length: a population-based prospective study. Ultrasound in Obstetrics and Gynecology. 2006; 27(4):362-367.

23. Cicero S, Skentou C, Souka A, To MS, Nicolaides KH. Cervical length at 22-24 weeks of gestation: comparison of transvaginal and transperineal-translabial ultrasonography. Ultrasound Obstet Gynecol [Comparative Study Research Support, Non-U.S. Gov't]. 2001; 17(4):335-40.

24. Yazici G, Yildiz A, Tiras M, et al. Comparison of transperineal and transvaginal sonography in predicting preterm delivery. Journal of Clinical Ultrasound. 2004; 32(5):225-230.

25. Orzechowski KM, Boelig RC, Baxter JK, Berghella V. A Universal Transvaginal Cervical Length Screening Program for Preterm Birth Prevention. Obstetrics & Gynecology. 2014; 124(3):520-525.

26. Marren AJ, Mogra R, Pedersen LH, et al. Ultrasound assessment of cervical length at 18–21 weeks' gestation in an Australian obstetric population: Comparison of transabdominal and transvaginal approaches. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2014; 54(3):205-255.

27. O'Hara S ZM, Sun Z. A Comparison of Ultrasounic Measurement techniques to measure the maternal cervix in the mid-trimester. Australasian Journal for Ultrasound in Medicine [Original Research]. 2015; 18(3):118-123.

28. Friedman AM, Srinivas SK, Parry S, et al. Can transabdominal ultrasound be used as a screening test for short cervical length? Am J Obstet Gynecol. 2013; 208(3):190.e1-190.e7.

29. To MS, Skentou C, Chan C, Zagaliki A, Nicolaides KH. Cervical assessment at the routine 23-week scan: standardizing techniques. Ultrasound in Obstetrics and Gynecology. 2001; 17(3):217-219.

30. Hernandez-Andrade E, Romero R, Ahn H, et al. Transabdominal evaluation of uterine cervical length during pregnancy fails to identify a substantial number of women with a short cervix. J Matern Fetal Neonatal Med. 2012; 25(9):1682-1689.

31. Saul LL, Kurtzman JT, Hagemann C, Ghamsary M, Wing DA. Is Transabdominal Sonography of the Cervix After Voiding a Reliable Method of Cervical Length Assessment? Journal of Ultrasound in Medicine. 2008; 27(9):1305-1311.

32. Nicholaides K. Fetal Medicine Foundation: Cervical Assessment on line Course [Internet]. Fetal Medicine Foundation: https://fetalmedicine.org/education/cervical-assessment: accessed 2012

33. Cutchie W. Cervical shortening and cervical insufficiency [Internet]. http://3centres.com.au/guidelines/complications-in-pregnancy-and-birth/cervical-shortening-and-cervical-insufficiency. Accessed 30 August 2012.

34. Callen PW. Limbach M, editor. Ultrasonography in Obstetrics and Gynaecology. 5th ed. Philadelphia: Saunders Elsevier; 2008.

35. Di Tommaso M, Berghella V. Cervical length for the prediction and prevention of preterm birth. Expert Review of Obstetrics and Gynecology. 2013; 8(4):345-355.

36. Mella MT, Berghella V. Prediction of Preterm Birth: Cervical Sonography. Seminars in Perinatology. 2009; 33(5):317-324.

37. Department of Health, The Women and Infants Research Foundation, The University of Western Australia, AMA, RANCOG, RACGP's. The Western Australian Preterm Prevention Initiative Western Australia: 2014.

38. Salomon LJ, Diaz-Garcia C, Bernard JP, Ville Y. Reference range for cervical length throughout pregnancy: non-parametric LMS-based model applied to a large sample. Ultrasound Obstet Gynecol. 2009; 33(4):459-64.

39. Iams JD, Goldenberg RL, Mercer BM, et al. The Preterm Prediction Study: Can low-risk women destined for spontaneous preterm birth be identified? Am J Obstet Gynecol. 2001; 184(4):652-655.

40. Berghella V, Roman A, Daskalakis C, Ness A, Baxter JK. Gestational age at cervical length measurement and incidence of preterm birth. Obstet Gynecol. 2007; 110(2 I):311-317.

41. The Royal Australian and New Zealand Collge of Obstetricians and Gynaecologists(RANZCOG). Measurement of cervical length for prediction of preterm birth 2017.

42. Lee HJ, Park, Tae Chul, Norwitz, Errol R. Management of Pregnancies With Cervical Shortening: A Very Short Cervix Is a Very Big Problem. Reviews in Obstetrics & Gynecolgy 2009; 2(2):107-115.

43. Newnham JP, Dickinson JE, Hart RJ, et al. Strategies to Prevent Preterm Birth. Frontiers in Immunology [Review]. 2014; 5: 584 doi: 10.3389/fimmu.2014.00584

44. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicentre, randomized, double-blind, placebo-controlled trial. Ultrasound in Obstetrics & Gynecology. 2011; 38(1):18-31.

45. Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol. 2018; 218(2):161-180.

46. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. Ultrasound Med Biol. 2015; 41(5):1126-47.

47. Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. Journal of the Acoustical Society of America. 2001; 110(1):625-634.

48. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med. 2013; 34(2):169-84.

49. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). Ultraschall Med. 2017; 38(4):e16-e47.

50. Hernandez-Andrade E, Hassan SS, Ahn H, et al. Evaluation of cervical stiffness during pregnancy using semiquantitative ultrasound elastography. Ultrasound Obstet Gynecol. 2013; 41(2):152-161 .

51. Swiatkowska-Freund M, Preis K. Elastography of the uterine cervix: implications for success of induction of labour. Ultrasound Obstet Gynecol. 2011; 38(1):52-56.

52. Hwang HS, Sohn IS, Kwon HS. Imaging analysis of cervical elastography for prediction of successful induction of labour at term. J Ultrasound Med. 2013; 32(6):937-46.

53. Molina FS, Gómez LF, Florido J, Padilla MC, Nicolaides KH. Quantification of cervical elastography: a reproducibility study. Ultrasound Obstet Gynecol. 2012; 39(6):685-689.

54. Wozniak S, Czuczwar P, Szkodziak P, et al. Elastography in predicting preterm delivery in asymptomatic, low-risk women: a prospective observational study. BMC Pregnancy and Childbirth [journal article]. 2014; 14(1):238.

55. Carlson LC, Hall TJ, Rosado-Mendez IM, Palmeri ML, Feltovich H. Detection of Changes in Cervical Softness Using Shear Wave Speed in Early versus Late Pregnancy: An in Vivo Cross-Sectional Study. Ultrasound in medicine & biology. 2018; 44(3):515-521.

56. Peralta L, Molina FS, Melchor J, et al. Transient Elastography to Assess the Cervical Ripening during Pregnancy: A Preliminary Study. Ultraschall in Med. 2017; 38(04):395-402.

57. Liu C, Li TT, Hu Z, et al. Transvaginal Real-time Shear Wave Elastography in the Diagnosis of Cervical Disease. J Ultrasound Med. 2019; 38(12):3173-3181.

58. Palmeri M, Feltovich H, Homyk A, Carlson L, Hall T. Evaluating the feasibility of acoustic radiation force impulse shear wave elasticity imaging of the uterine cervix with an

intracavity array: a simulation study. Ultrasonics, Ferroelectrics, and Frequency Control, IEEE Transactions on. 2013; 60(10):2053-2064.

59. Carlson LC, Feltovich H, Palmeri ML, Rio AMd, Hall TJ. Statistical analysis of shear wave speed in the uterine cervix. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control. 2014; 61(10):1651-1660.

60. Peralta L, Mourier E, Richard C, et al. In Vivo Evaluation of Cervical Stiffness Evolution during Induced Ripening Using Shear Wave Elastography, Histology and 2 Photon Excitation Microscopy: Insight from an Animal Model. PloS one. 2015; 10(8):e0133377-e0133377.

61. Carlson LC, Romero ST, Palmeri ML, et al. Changes in shear wave speed pre- and post-induction of labour: a feasibility study. Ultrasound in Obstetrics & Gynaecology. 2015; 46(1):93-98.

62. Muller M, Aït-Belkacem D, Hessabi M, et al. Assessment of the Cervix in Pregnant Women Using Shear Wave Elastography: A Feasibility Study. Ultrasound in Medicine & Biology. 2015; 41(11):2789-2797.

63. Hernandez-Andrade E, Maymon E, Luewan S, et al. A soft cervix, categorized by shear-wave elastography, in women with short or with normal cervical length at 18-24 weeks is associated with a higher prevalence of spontaneous preterm delivery. J Perinat Med. 2018; 46(5):489-501.

64. Rosado-Mendez IM, Carlson LC, Woo KM, et al. Quantitative assessment of cervical softening during pregnancy in the Rhesus macaque with shear wave elasticity imaging. Physics in medicine and biology. 2018; 63(8):085016-085016.

65. Agarwal S, Agarwal A, Joon P, Saraswat S, Chandak S. Fetal adrenal gland biometry and cervical elastography as predictors of preterm birth: A comparative study. Ultrasound (Leeds, England). 2018; 26(1):54-62.

Chapter 2

Reliability Indicators for 2D Shear Wave Elastography

2.1 **Abstract**

Ultrasound shear wave technology providers have either point shear wave or two dimensional shear wave elastography available on their ultrasound systems. With two dimensional shear wave larger regions of interest can be interrogated, with both the main acoustic radiation pulses and the resultant shear waves potentially being affected by ultrasound artifacts. Some providers assist the sonographer with elastogram maps indicating the reliability or precision of the shear wave propagation. This chapter explores the importance of the consideration of the precision maps and standard deviation output available on some devices, and the implications for conversion of shear wave speed to pressure.

Keywords Shear wave, elastography, reliability, two dimensional, ultrasound

2.2 **Background**

Shear wave elastography uses ultrasound technology to quantify the stiffness of tissues in the region being assessed. The basic premise being that the ultrasound pulse used in B-mode imaging is modified to become a low frequency/high intensity push pulse often called an acoustic radiation force impulse (ARFI).[1] This ARFI produces small tissue movements in the plane of the push pulse that creates shear waves that move in a sideways direction away from the push pulse.[1] The momentum of the push pulse is transferred to the tissues, causing a propagation of the shear wave through the medium by way of attenuation mechanisms such as absorption and scattering.[2] The speed of shear wave movement is slow compared to the speed of the ultrasound pulses and this movement can be tracked by the ultrasound machine.[3] The movement of the shear wave is tracked by tracking pulses in a similar method to Doppler technology, with ultrasound vendors employing different methods to determine shear wave arrival time.[2,4] A typical time of flight method is to estimate the speed of the shear wave arrival time at positions lateral to the region of excitation created by the push pulse. A linear regression of time versus the position of the data within a kernel is performed to determine the shear wave speed.[2]

Relative stiffness of the tissue is quantified in two ways. The shear wave speed (SWS) obtained in metres per second (m/s) is the 'raw' data and indicates the speed of shear wave propagation; this can be mathematically converted to a measure of tissue elasticity output in kilopascals (kPa).[1] Most shear wave technology providers convert the shear wave speed to kPa ($kPa = speed^2 \times 3$).[5] The conversion of SWS to kPa makes the assumption that the region being interrogated is isotropic, homogeneous and exhibits linear behavior; hence the sonographer should be aware that biological tissues may break the assumptions used in this calculation.[5]

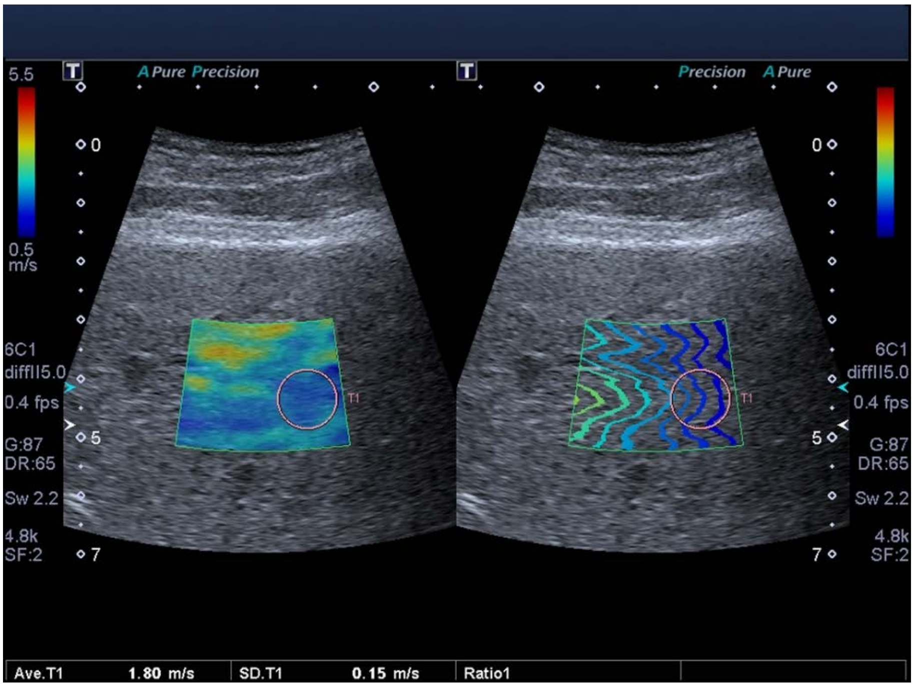


Figure 2.1: 2D SWE elastogram placed in the right lobe of the liver showing an elastogram and propagation map, with a mean speed of 1.80m/s and SD of 0.15m/s at region T1.

Point shear wave (pSWE) technology investigates regions of tissue whereby one or two push pulses are used to produce shear waves in a small and fixed region of interest (ROI).[5] Many ultrasound vendors now provide two dimensional shear wave technologies (2DSWE) and 2DSWE differs from pSWE in a number of ways. Larger regions of interest can be interrogated using 2DSWE. As can be seen in Figure 2.1, in 2D SWE a colour elastogram box can be placed over a larger region of tissue. The colour of the elastogram is a qualitative representation of the tissue stiffness, and it is possible to place multiple ROI's within the elastogram to obtain the quantitative measurements of SWS or tissue elasticity. A recent update to the guidelines on the use of elastography from the World Federation of Ultrasound in Medicine and biology recommended that one ROI be placed per elastogram.[6] To achieve the larger elastogram used in 2D SWE, multiple push pulses and tracking pulses are being applied at finite distances across the elastogram. Some vendors focus the push and tracking pulses at a specified depth into the elastogram, whilst others such as supersonic shear imaging (SSI) push multiple pulses down each line of sight to produce a Mach cone effect throughout the elastogram.[1]

2.3 Shear wave reliability

An assumption of the time of flight tracking methods used to estimate SWS is that the tissue in the region of interest is homogeneous.[2] In soft tissues this assumption of homogeneity can be violated, creating speed artifacts.[2] The precision or reliability of the shear wave propagation can be affected by a number of factors. The transmission of the main pushing pulses can be affected by the strength of the pulse and variation in tissue density, and can be prone to acoustic attenuation, absorption, reflection and scatter. Shear wave production can also be affected by scatter, reflection, refraction and anisotropic tissues, resulting in errors in SWS estimation.[5] The larger elastogram in 2D SWE uses multiple push pulses across the elastogram over larger regions of tissue and there may be tissue inconsistencies across the region of the elastogram, and also in the elevation plane of the transducer that can affect the speed of shear wave propagation.[4] SWS measurements can also be affected by random errors such as jitter in the displacement tracking of the ultrasound device.[4]

2D SWE technology providers supply the sonographer with indications of the reliability of shear wave propagation unique to each vendor. The GE (Chicago, Illinois, United States) system recommends that the colour elastogram box should have greater than 50% of colour filling for shear wave propagation to be considered reliable. The Philips Epiq (Amsterdam, Netherlands) uses a confidence map, and Siemens (Erlangen, Germany) technology a quality map, whereby red regions are considered to have unreliable values, green regions the most accurate and yellow regions less than optimal. The Canon (Otawara, Tochigi, Japan) technology uses wave front maps to indicate the reliability of shear wave propagation with parallel equidistant lines indicating reliable shear wave propagation.[3] The propagation map on the Canon device also gives an indication of the speed of shear wave propagation. The closer the lines are together the slower the SWS, with a greater distance between and widening of the lines indicating faster SWS.

It has been recommended that a 10mm ROI is used to acquire the mean speed or kPa for the assessment of liver stiffness.[3] Within the 10mm ROI many values of speed of shear wave propagation are being obtained, and the mean speed is displayed. The many hundreds of values of shear wave speed obtained are mathematically converted to a kPa value, and the mean kPa value can be displayed on elasticity elastogram maps. Most 2D SWE providers also display the standard deviation (SD) of the values obtained within the ROI, with SSI technology also displaying the minimum and maximum values registered within the data set.

The fact that a mean (or average) value of SWS is quoted indicates immediately that not all the measured values of SWS are the same, that there is a level of variation between these values, and an average value provides an indication of where the collection of values is generally located on the scale of SWS. In the context of a perfect measuring instrument making multiple measurements of an inanimate object maintained in a constant environment, then, whether 10 measurements or 10 000 measurements were taken, there would be an expectation that all those values would be identical; however this is rarely the case. Not all these values will be identical, and so account needs to be taken of the extent of variation or scatter that is present in the set of measurements. The formal name for this is the variance. It is calculated by expressing the distance each individual is from the mean value (i.e., as a deviation from the mean = value - mean), squaring those deviations (because values smaller than the mean will produce negative deviations, values larger than the mean will produce positive deviations), adding them all together and calculating an average. The square root of this variance is the SD. In other words, it is the root mean squared deviation about the mean. The SD quantifies the amount of scatter or dispersion present in a set of values; the larger the SD the greater the scatter, and the smaller the SD the less the scatter. The perfect instrument above would produce an SD of zero. Fisher's Information is inversely proportional to variance,[7] the smaller the variance the better the information.

Thus the SD can give the sonographer a further indication of the reliability of shear wave propagation. The Canon 2D SWE technology can be used as an example: A recommendation from Canon Medical is that nearly 1000 values of speed are obtained from a 10mm circle ROI and the mean and SD of these values is displayed. Regions within the elastogram that have the most uniform colour will be concordant with regions within the wave front map exhibiting the straightest, most parallel and equidistant propagation lines. These regions will also output the lowest SD. Regions of non-uniform colour and distortion of propagation lines are indicative of artifacts affecting reliable shear wave propagation resulting in unreliable shear wave speeds. These regions also exhibit a high value of SD. As can be seen in Figure 2.2, the T1 ROI has a uniform elastogram and wave front map and registers a mean speed of 1.70m/s with and SD of 0.12m/s. Adjacent to this the T2 ROI has been placed in a region of non-precise shear wave propagation indicated by the non-uniform elastogram and erratic wave front map. The distance between the wave front lines is also increased in this region and an increased mean speed of 2.98m/s and a much higher SD value of 0.66m/s has been obtained.

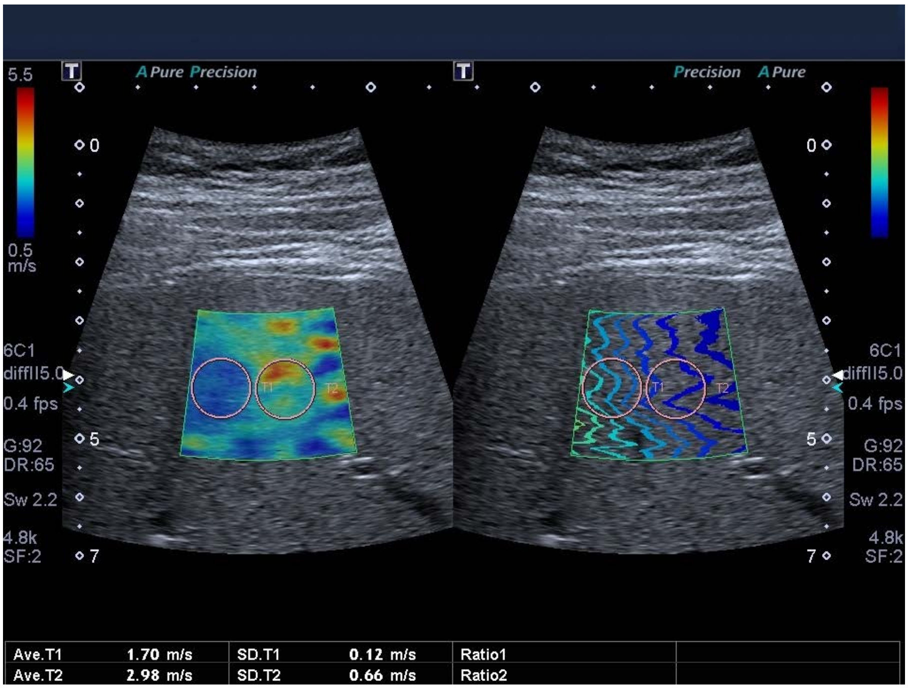


Figure 2.2: 2D SWE elastogram shown in a region of the liver exhibiting uniform propagation map and elastogram at T1 with a mean speed of 1.7m/s and SD of 0.12m/s, and non-uniform propagation map and elastogram at T2 with a mean speed of 2.98m/s and SD of 0.66m/s.

Though unlikely to occur, if as an example a strong assumption is made that a symmetrical (normal) distribution of the nearly 1000 values obtained within a 10mm ROI has been achieved, the mean median and mode values for the data set will be identical or very similar, with a symmetrical spread of speeds around these central values. As illustrated in Figure 2.3, if the mean speed obtained is 1.5m/s with an SD of 0.05 (3% of the mean), the central 68% of the speed values obtained (mean $\pm$ 1 SD) will range between 1.45 and

1.55m/s, and 99.865% of the values (mean $\pm$ 3 SD) will range between 1.35 and 1.65m/s, demonstrating a very narrow range of values for the entire dataset, and high reliability for the mean. If the SD was 0.5 (33% of the mean) then the central 68% of values would range between 1.0 and 2.0m/s, and 99.865% of the values would be ranging between 0 and 3m/s. Thus a high SD is indicative of a large variation of SWE speed values being obtained within the ROI, and the central mean value becomes less reliable as an indicator of tissue stiffness in this region due to the large variation of speeds being obtained.

The calculation of probable ranges outlined above depends principally on two assumptions, namely independence between observations and conformity with the normal distribution. Independence implies that the values of any one observation could not affect, nor have been affected by, the value of any other observation. Given that a set of SWS values are sourced from the same liver in the same patient by the same machine in a single session over a short period of time, then the independence requirement cannot be met, leading to levels of variation that are likely to be less than would otherwise have been. Consequently, any range defined by (mean $\pm$ n SD's) will produce a fraction that will be slightly smaller than its normal equivalent. This should not deter the consideration and use of such fractions because, within the current context, it is expected that the associated under-evaluation will be consistent, and so remain useful as a guide for sonographers.

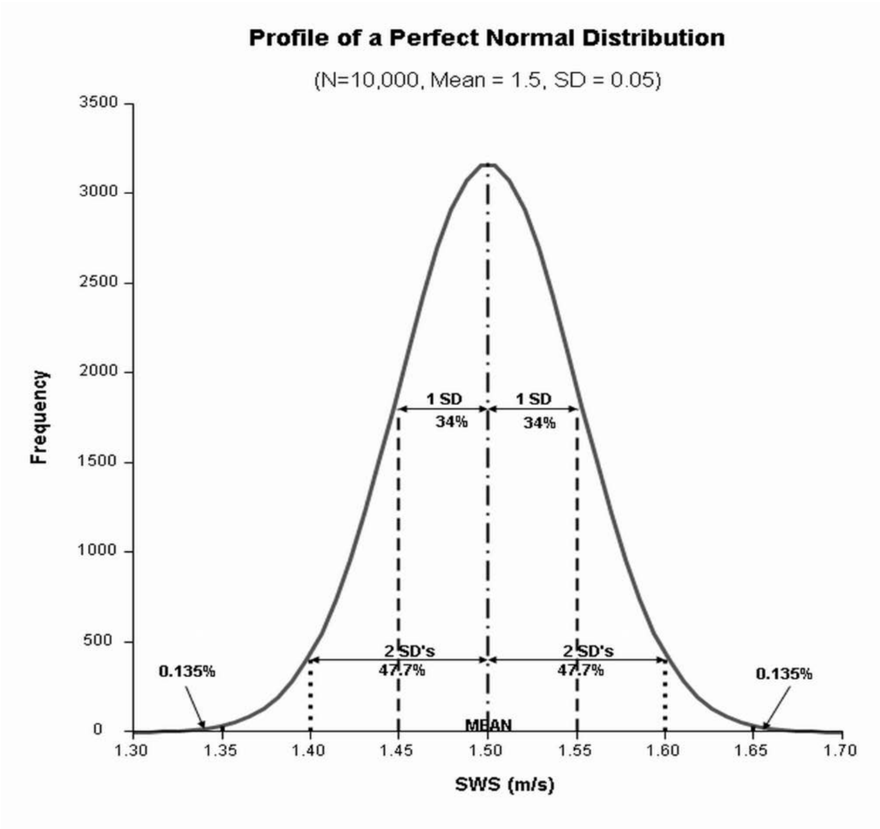


Figure 2.3: Illustration of a normal or symmetrical distribution of values in a data set of 10,000 values exhibiting a mean value of 1.5 and SD of 0.05.

Conformity with the normal implies the property of symmetry. In statistical parlance this is the coefficient of skewness, and has a value of 0 if the distribution is symmetrical about the mean. This is unlikely to be the case when the mean SWS have a low value, say 0.1 for illustration purposes. If the SD is 0.05, as before, then the deviate (mean – 2 SD's) corresponds to an SWS of (0.1 – 2 x 0.05) = 0, implying that 97.7% of the SWS values are greater than 0 and that the remaining 2.3% are less than 0. Also, the deviate (mean – 3 SD's) corresponds to an SWS of (0.1 – 3 x 0.05) = -0.05.

Theoretically the normal distribution ranges from -∞ to +∞, but shear wave speeds cannot be negative. Consequently, for SWS distributions, 0 m/s constitutes a lower domain boundary, and 100% of all SWS values will be greater than 0 (ignoring the exact value of 0, corresponding to total acoustic impedance.) With this 'out of bounds' zone at the left-hand end of the distribution, the only 'room' for expansion of the range of values is at the right-hand or high end of the distribution. Consequently, the distribution will become asymmetrical, exhibiting a long tail to the right, known as positive skewness, and will no longer be normal. In a positively skewed data set the mean will be different from the median and mode values and this will invalidate the use of the $\pm$ symbol as used in the above examples. If the skewness is only slightly positive, then, for all practical purposes, the normal method would probably suffice. If not, then the data would be better described by the gamma distribution. This is commonly used in the distributions of rates (and speed is a rate) where negative values are not possible.[8] However, computations involving the gamma distribution are considerably less 'rule of thumb' than the normal. See Figure 2.4 for comparison. The mean, median and mode are no longer coincident, and the same ordinates (at mean-SD and at mean+SD) now account for different (and unequal) proportions of the population of values.

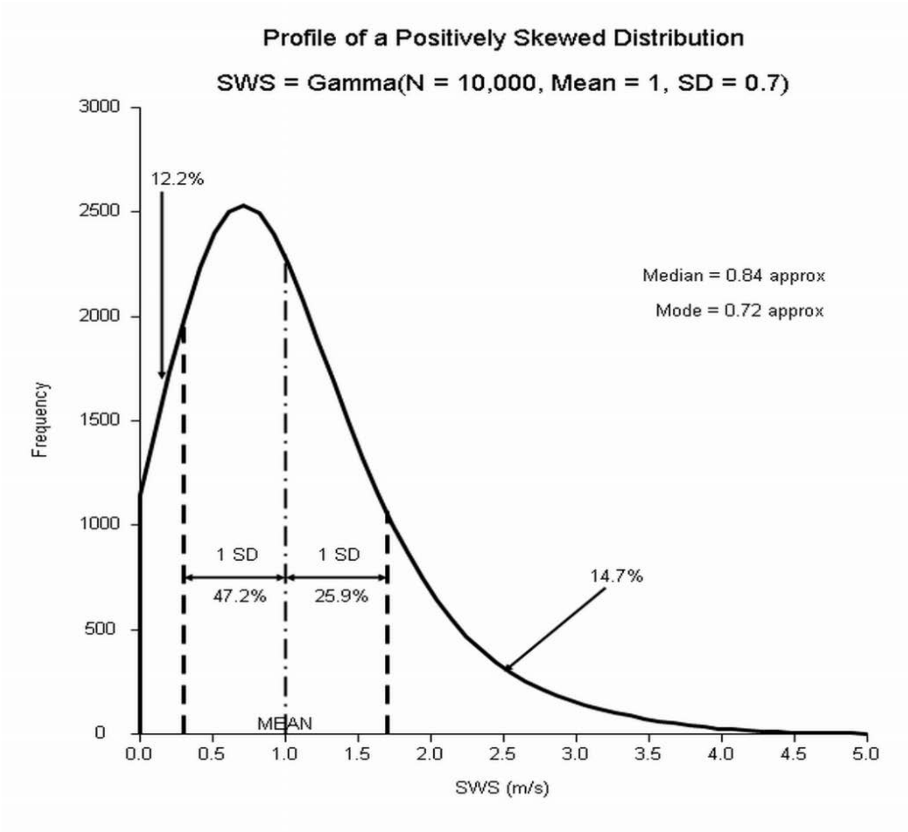


Figure 2.4: Example of a skewed distribution. The mean, median and mode are no longer coincident, and the same ordinates (at mean-SD and at mean+SD) now account for different (and unequal) proportions of the population of values

In practice two phenomenon have been observed when undertaking liver shear wave elastography examinations. It can be observed that adjacent regions in the same patient may have differing values of SD, but still return a similar mean speed. Regions with a non-uniform elastogram colour, erratic wave front map and higher SD have also been observed to have much higher mean SWS than adjacent regions as can be seen in Figure 2.2, with a widening of the distance between the wave front lines also being observed in this region. To this end we have performed a scatterplot of the mean SWS and the SD for each value obtained on six patients attending for liver assessment (Figure 2.5). All measurements were acquired using the Canon Aplio 500 (Otawara-shi, Tochigi, Japan) shear wave technology. These scatterplots shows an overall trend of increasing SWS with increasing SD for each participant, with some patients displaying similar mean speed with increasing SD.

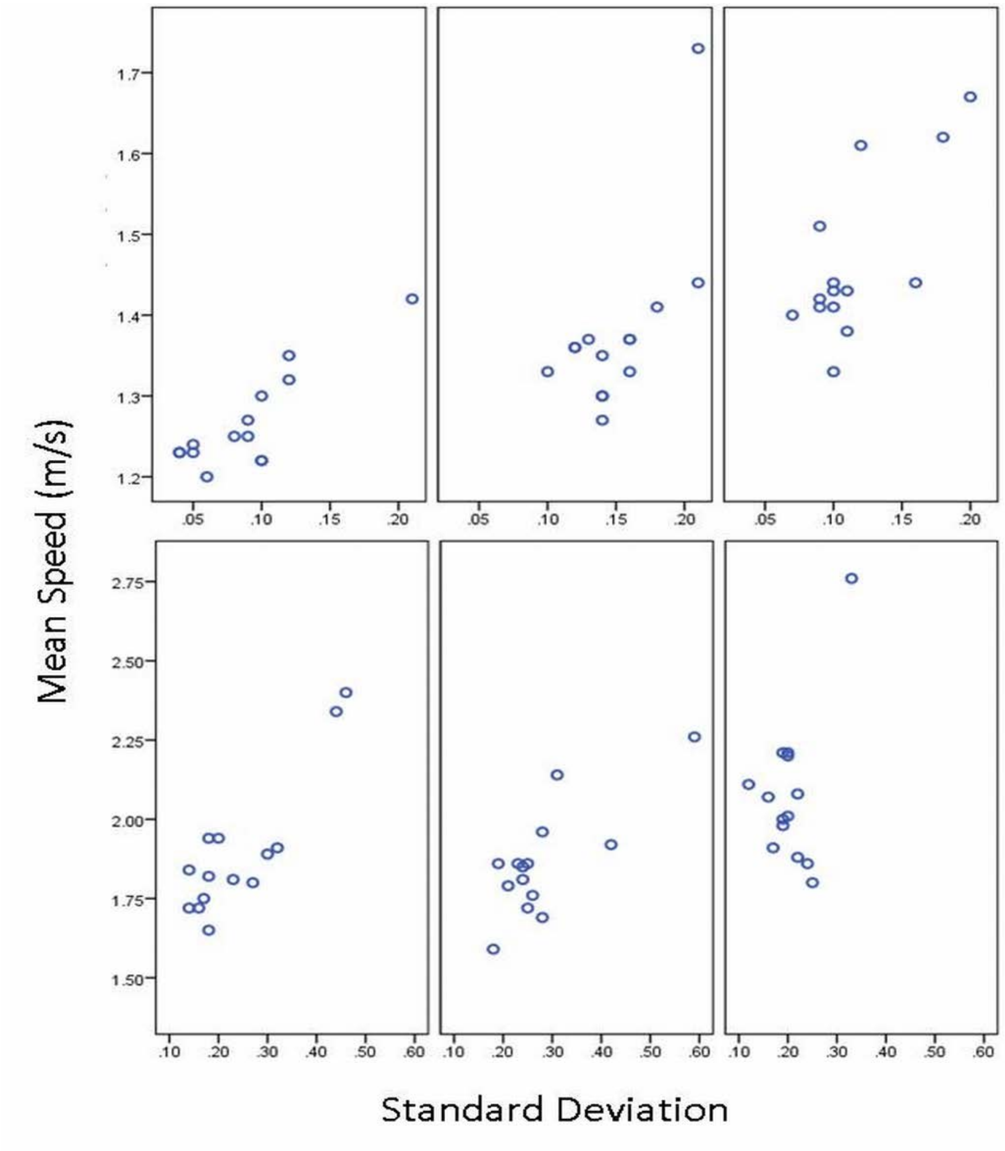


Figure 2.5: Scatterplots demonstrating the mean speed and standard deviation obtained for each value for six patients undergoing shear wave elastography of the liver.

2.4 **Conversion of speed to pressure**

Consideration of the SD is also important for the conversion of the shear wave speed in m/s to elasticity in kPa. As shown in Figure 2.6, a mean speed of 1.36m/s with an SD of 0.12m/s has been obtained. The kPa value calculated by the ultrasound machine is shown to be 5.4kPa. By converting the mean speed of 1.36m/s to kPa using the mathematical conversion of $speed^2 \times 3$,[1,5] the value will be 5.5kPa. This small difference can be explained by the fact that the nearly 1000 values of SWS in a 10mm ROI are all being converted to kPa before a mean value is calculated, and as this range of values as signified by the SD reading is quite small, the values are minimally different from a mathematical conversion of the mean value alone. Observing the values in Figure 2.7, the mean SWS of 1.36m/s has also been obtained but with a large SD of 0.94, thus as explained previously a much greater range of SWS values has been obtained in the ROI. The transformation of this larger range of SWS values to kPa has resulted in a kPa value of 10.3 being obtained. The resultant values would have different outcomes for the patient with the SWS value of 1.36m/s considered to be in the normal range for liver stiffness, with the kPa value of 10.3 being at a level of significant fibrosis.

	Speed[m/s]		Elasticity[kPa]		
	Average	SD	Average	SD	Depth[cm]
8	1.35	0.14	5.4	1.1	4.0
9	1.39	0.09	5.7	0.8	3.8
10	1.36	0.12	5.4	1.0	3.8
11	1.28	0.10	4.7	0.8	3.6
12	1.42	0.11	6.0	1.0	3.6

Figure 2.6: **Shear wave elastography report page demonstrating five values of shear wave speed and the calculated kPa values. These values exhibit a low SD and the conversion to kPa is similar to a direct conversion of just the mean value.**

	Speed[m/s]		Elasticity[kPa]		
	Average	SD	Average	SD	Depth[cm]
1	1.83	1.10	15.9	12.9	5.3
2	1.36	0.94	10.3	10.2	6.2
3	1.45	0.65	8.3	6.0	5.7
4	1.27	0.48	6.0	2.8	5.8

Figure 2.7: Shear wave elastography report page demonstrating four values of shear wave speed and the calculated kPa values. These values exhibit high SD and the conversion to kPa has a large discrepancy with a mathematical conversion of the mean speed value to kPa alone.

When using the Canon shear wave technology it has been recommended that the value of the SD is kept to less than 20% of the mean speed. Researchers at the Royal Melbourne Hospital have found that an SD that was greater than 15% of the mean speed showed low reliability and deviated by significant amounts from the median value obtained for the diagnosis of liver fibrosis.[7]. This percentage of the SD to the mean of the SWS does not have a linear correlation with the SD obtained when these values are converted to kPa. As can be observed in Figure 4 the value of 1.36m/s with an SD of 0.12m/s, the SD equates to approximately 9% of the mean value. The conversion to kPa has a mean of 5.4kPa and an SD of 1kPa, with the SD now equating to 18% of the mean value. Thus, the consideration of obtaining a low SD in 2D SWE imaging is most relevant when obtaining shear wave speed.

2.5 **Conclusion**

The reliability of shear wave propagation can be affected by ultrasound artifacts and the use of indicators of reliability provided by ultrasound vendors should include the inspection of the standard deviation of the mean shear wave speed. These factors are important to assist the sonographer in effective placement of the region of interest, and should be regarded as important considerations when using two dimensional shear wave elastography for the assessment of tissue stiffness.

2.6 **References**

1. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med. 2013; 34(2):169-84.

2. Rouze NC, Wang MH, Palmeri ML, Nightingale KR. Parametres Affecting the Resolution and Accuracy of 2D Quantitative Shear Wave Images. IEEE transactions on ultrasonics, ferroelectrics, and frequency control. 2012; 59(8):1729-1740.

3. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). Ultraschall in Med.

4. Wang M, Byram B, Palmeri M, Rouze N, Nightingale K. On the precision of time-of-flight shear wave speed estimation in homogeneous soft solids: initial results using a matrix array transducer. IEEE transactions on ultrasonics, ferroelectrics, and frequency control. 2013; 60(4):758.

5. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. Ultrasound Med Biol. 2015; 41(5):1126-47.

6. Wang M, Byram B, Palmeri M, Rouze N, Nightingale K. On the precision of time-of-flight shear wave speed estimation in homogeneous soft solids: initial results using a matrix array transducer. Ultrasonics, Ferroelectrics and Frequency Control, IEEE Transactions on. 2013; 60(4):758-770.

7. Kenney J.F. and Keeping E.S., Mathematics of Statistics, 1951, Van Norstrand.

8. Gamma Distribution. 12 September 2018, 21:49 UTC. In Wikipedia: The Free Encyclopedia. Wikimedia Foundation Inc. Encyclopedia on-line.

9. Nadebaum DP, Nicoll AJ, Sood S, Gorelik A, Gibson RN. Variability of Liver Shear Wave Measurements Using a New Ultrasound Elastographic Technique. Journal of Ultrasound in Medicine. 2018; 37(3):647-656.

Chapter 3

Shear wave elastography on the uterine cervix:

Technical development for the transvaginal approach

3.1 **Abstract**

Objectives This research aimed to identify biological and technical confounders in the cervix when applying shear wave elastography with an endovaginal transducer to non-gravid patients.

Methods Cervical speed measurements were obtained at the internal and external os, anterior and posterior portions of the cervix using a transvaginal approach in 69 non-gravid patients.

Results Reliable measurements were obtained at the external os and internal os, anteriorly and posteriorly, in 63, 55, 55 and 26 patients respectively. The mean speed obtained at the external os, anteriorly and posteriorly, was 2.52 ± 0.49m/s and 2.87 ± 0.63m/s respectively, and at the internal os anteriorly and posteriorly, 3.29 ± 0.79m/s and 4.10 ± 1.11m/s respectively. The difference in speed between all regions was statistically significant ($p<0.05$).

Conclusion Ultrasound induced artifacts appear to affect the transmission of the elastographic main pulse, with cervical position contributing to suboptimal shear wave production in the posterior cervix. Reliable shear wave propagation can be achieved in the anterior cervix in most patients.

Keywords Shear wave, elastography, cervix, preterm birth, transvaginal ultrasound

3.2 Introduction

Retention of a pregnancy requires the cervix to maintain strength to withstand multiple forces from the uterus, from the weight of the growing fetus and amniotic sac, and also passive pressure from the uterine wall. The cervix softens and shortens throughout pregnancy and finally dilates for the fetus to be delivered vaginally. Premature softening of the cervix is associated with early shortening of cervical length and subsequent spontaneous preterm birth (SPTB).[1] The cervix can be described as soft, firm or medium based on a digital examination, but this method is subjective to the clinician, and creates difficulties due to the expectation that the cervix will soften initially at the proximal portion.[1]

Currently, cervical length obtained using transvaginal ultrasound (TVU) is the feature that is used to indicate cervical strength and premature softening.[2] A short cervix has been shown to be a significant risk factor for subsequent SPTB.[3] In women with a high risk of SPTB due to medical history, a shortened cervical length on TVU has a sensitivity of over 50% for subsequent SPTB. However, in low risk women the sensitivity is reduced to 37%,[4,5] and the appropriate method for screening for SPTB in these women is yet to be established. With preterm birth affecting 13 million babies every year and the implications for neonatal mortality and morbity,[6] there is a need for a technique to assess cervical strength with greater sensitivity than length alone.

Ultrasound elastography assesses mechanical properties of tissues in the region being examined. The basis for this technique is that soft tissue deforms differently from firm tissue and the elastographic images reflect this difference.[7] Utilising strain elastography, it has been proposed it may be possible to identify women in the historically low risk who are at an increased risk of SPTB due to softening of the cervical tissues which precedes a reduction in cervical length.[8] A more successful induction of labour has also been observed in patients with a softer internal os.[9]

When applied to the cervix, elastography techniques based on strain imaging have difficulties due to the lack of surrounding reference tissue and the inability to reliably quantify, and hence reproduce, transducer pressure applied to the cervix.[10] Shear wave elastography (SWE) produces an acoustic radiation force impulse (ARFI) excitation to produce shear waves.[11] By quantifying parameters related to the propagation of the shear wave, such as shear wave speed, one can infer an estimate of tissue stiffnes.[6] It is expected that this technique will produce a more objective and reproducible mechanical evaluation of the cervix than strain elastography.[12,13]

There is evidence to support the use of SWE on the maternal cervix during pregnancy to assess cervical strength. [14-16] It has been shown that it is feasible to examine the external os anteriorly with TVU SWE and that a reduction in speed in this region is evident in women who deliver preterm.[14] It has also been shown with SWE that the cervix softens as gestational age advances,[15] and in women who have cervical ripening following induction of labour.[16] The cervix has been shown to be softer during pregnancy than in the non-gravid state.[1] An increase in stiffness in the cervix has been shown in the region of cervical carcinoma with the use of strain elastography.[17] This study investigates the use of shear wave elastography with an endovaginal ultrasound technique applied to the non-gravid human uterine cervix. Experimentation and technique development was performed on a low risk non-gravid population. The goal being to identify biological and experimental variables that affect the interpretation of shear wave speed (SWS) estimates in the non-gravid population, to contribute to the standardisation of the technique for application in the non-gravid population, and in the main part to the gravid cervix. With the consideration that there may be some differences observed in the technique applied in the obstetric population due to extrinsic pressure from fetal parts at the internal os.

3.3 Material and Methods

This pilot study was conducted at branches of SKG Radiology in Perth, Western Australia. A convenience sample was utilised from women presenting for a routine gynaecological ultrasound. All participants were between 18 and 49 years of age, menstruating regularly with varying pregnancy history and ethnicity. All patients were required to read a patient information form and give informed consent before being enrolled in the study. Ethics approval was granted from the clinical site and the Curtin University Human Research Ethics Committee.

Data collection occurred over a 13 month period commencing in July 2016. Estimation of sample size was performed with consultation from a statistician. The research by Carlson et al [16] identified a statistically significant difference between the stiffness of cervical tissue in ripened and unripened hysterectomy specimens of the cervix utilising SWE. The difference between the mean values and the standard deviations of the values were utilised to formulate a sample size using the equation for Samples Sizes for Comparative Research Studies by Eng. [18] A level of significance of $p<0.05$ was utilised. This calculation resulted in a minimum of 50 normal (stiff/non-gravid) cervix needed to formulate a baseline cervical stiffness for non-gravid patients.

3.3.1 Imaging protocol

All imaging was performed on the Toshiba Aplio 500 versions 6 and 6.5 ultrasound machines (Otawara-shi, Tochigi, Japan). Cervical stiffness measurements were acquired using the 11C3 PVT-781VTE intra-cavity transducer. The machine setting of a shear wave frequency of 4MHz, tracking of 0 was employed. This setting utilises a 4MHz push pulse and 4MHz tracking pulse. SWS measurements were obtained using continuous mode and the lowest frame rate setting of 1, equating to 0.4 frames per second. The elastogram map was stable for at least 3 seconds before speed measurements were obtained.[19]

Measurements were registered in the mid-sagittal plane of the uterine cervix, midway between the canal and serosa at the internal and external os, anterior and posterior. This plane was used as it allows sonographers to identify the required anatomical landmarks. Once in contact with the cervix, the transducer was withdrawn to minimise transducer pressure on the cervix whilst not compromising the B-mode image.

For inter-operator testing the primary SWE sonographer had over 20 years of experience in the field of sonography with two secondary operators having less than and more than 5 years of experience, respectively. Both secondary sonographers underwent training in the technique before commencement of data collection. The primary and senior secondary sonographers are both skilled in liver shear wave elastography and all sonographers have experience in gynaecological and obstetric applications of ultrasound.

3.3.2 Imaging methodology

3.3.2.1 Elastogram Map Placement

The elastogram map opacity was set to 0.3 to allow for visualisation of the cervical anatomy through the elastogram. Using a methodology similar to other authors initially,[10,15] (the first eight participants) the elastogram map was placed over the entire length of both anterior and posterior portions of the cervix, with placement of all four regions of interest simultaneously to obtain speed measurements (Figure 3.1). Utilizing a large elastogram box resulted in difficulties in focusing the region of greatest sensitivity of the main pulse to the region of interest (ROI). The recent EFSUMB update on the use of liver ultrasound elastography recommends that the main pulse focus should be placed at the level of the ROI.[20]

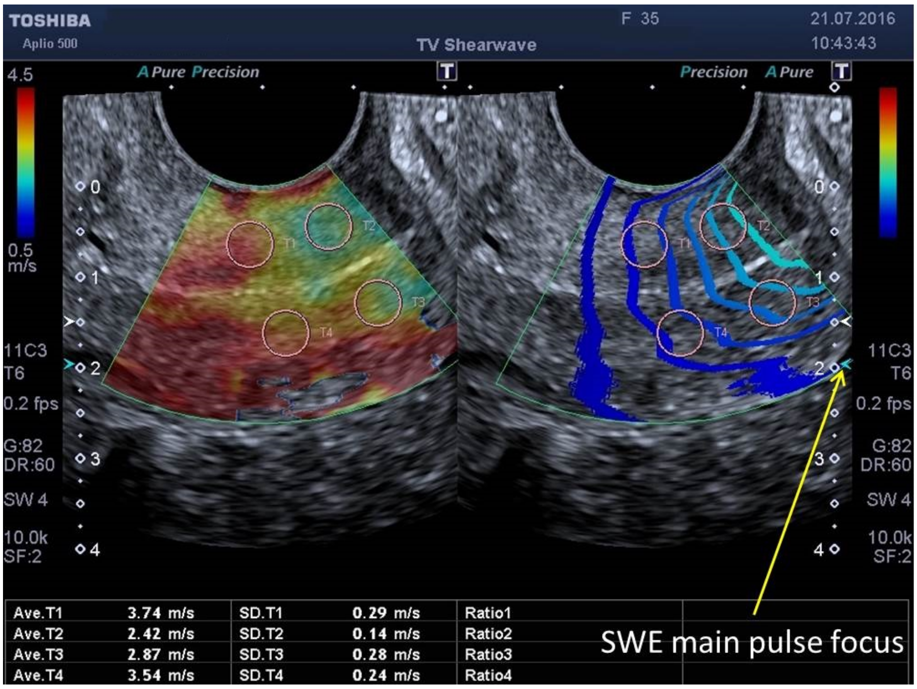


Figure 3.1: Large elastogram displaying placement of four ROI's in the different regions of the cervix being interrogated and the arrow highlighting the region of greatest sensitivity of the SWE main pulse.

To improve shear wave propagation and repeatability,[20] the authors reduced the elastogram box size to an anterior-posterior (AP) dimension of 15mm and the bottom width of the box was set to 20mm. The focus was set to the centre of the elastogram box at the level of intended ROI placement. Each part of the cervix was interrogated separately so that the region of greatest sensitivity could be positioned more effectively to the anterior and posterior uterine cervix for both internal and external os (Figure 3.2).

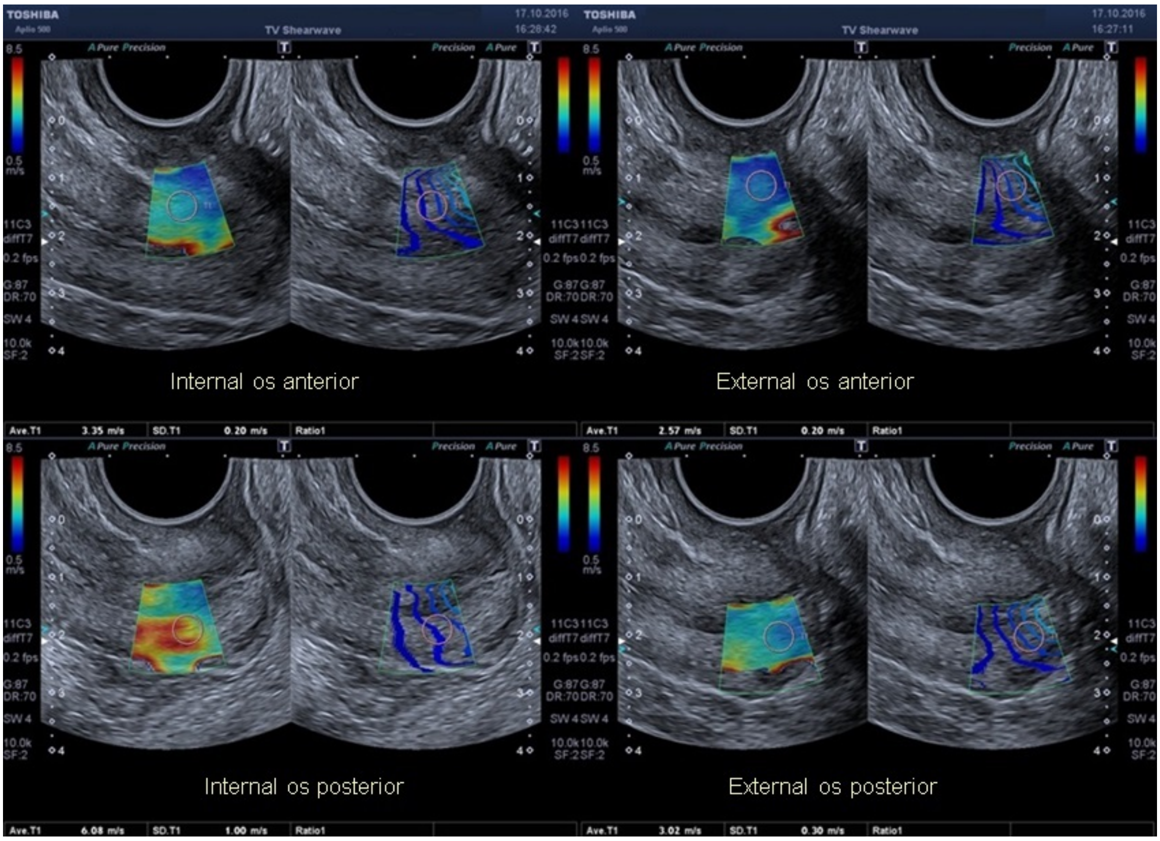


Figure 3.2: Cervical SWE with reduced elastogram size and a 5mm ROI, showing separate interrogations at each region of the cervix, with mean speeds for the internal os anterior

and posterior of 3.35m/s and 6.08m/s, and for the external os anterior and posterior of 2.57m/s and 3.02m/s respectively.

3.3.2.2 Shear wave region of interest placement

In the non-gravid state, the uterine cervix measures approximately 25mm in length and 20 to 25mm in total width, equating to an approximately 10mm width of collagenous and smooth muscle tissue around the central canal.[21] Histological evidence shows that the cervical canal is surrounded by a layer of longitudinal smooth muscle fibres adjacent to the canal. Wrapping circumferentially around the longitudinal layer is a layer of smooth muscle and collagenous cells (Figure 3.3). At the internal os there is a 50-60% concentration of smooth muscle cells in the circumferential layer, reducing to 40% at the mid cervix, and to 10% at the external os,[22] with no appreciable difference in this structure between nulliparous and multiparous specimens.[22] The longitudinal fibres are thought to be responsible for the action of cervical effacement and the circumferential layer to prevent cervical dilatation.[21] It has been hypothesised that the circumferential layer may be acting as a 'sphincter' to retain pregnancy.[21,22] A 5mm ROI (Figure 3.2) has been utilised for this study to facilitate ROI placement in the circumferential layer of collagen and smooth muscles thought responsible for pregnancy retention.

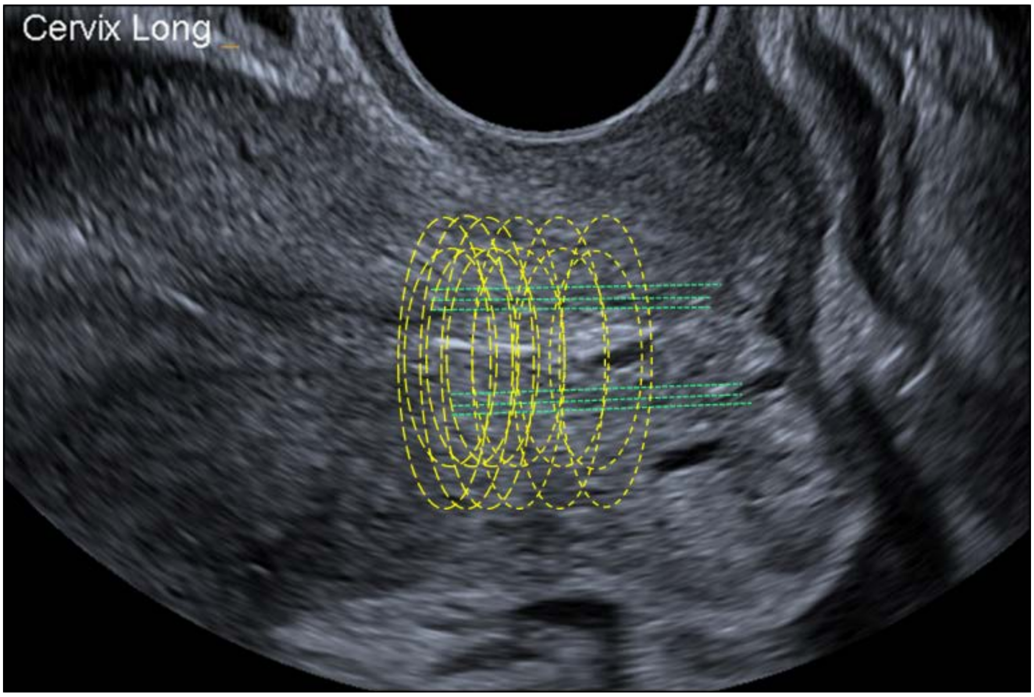


Figure 3.3: Ultrasound image of the uterine cervix demonstrating the central layer if smooth muscle fibres running parallel to the cervical canal and the circumferential layer of smooth muscle and collagenous fibres where the ROI is placed for SWE sampling.

3.3.2.3 Shear wave precision

Utilizing Toshiba technology, the precision of the shear wave propagation can be assessed in a number of ways. This elastogram speed map was set to a scale of 0.5 to 8.5cm/s with blue being indicative of softer tissues. Regions of heterogeneous colour or loss of colour indicate a loss of precise shear wave propagation. A red band of colour in the near field and extending into the elastogram map is indicative of increased transducer pressure on the skin or organ and vertical artifacts through the elastogram are indicative of transducer movement. As with B-mode ultrasound imaging, shear waves are also prone to scattering, reflection or refraction and these artifacts further affect the precision of shear wave speeds.[24] Planar wave propagation is an assumption in the estimation of SWS. The validity for this assumption can be tested using the waveform propagation maps provided by the scanner. The wave front propagation map is unique to Canon technology and indicates shear wave arrival time as represented by contour lines. The shear wave arrival time is inversely related to the material stiffness, and thus wider spacing indicates a faster shear wave, and therefore, a stiffer material. The contour maps also indicate precision of shear wave propagation. Regions of highest precision are those where the contour lines are shown to be parallel and equidistant, with a loss of parallel lines being indicative of non-planar shear wave propagation. Due to the curvature of the intra-cavity transducer face, there is some divergence of these parallel lines. This effect would be more apparent in the far field of the elastogram box.

The ROI also gives indications of the precision of the shear wave propagation. Many hundreds of values are obtained from the 5mm ROI and the mean speed and one standard deviation (SD) of these values is displayed. The regions within the elastogram with the most homogenous colour and straightest, most parallel and equidistant propagation lines will also correlate with the lowest SD of the mean. Regions of heterogeneous or loss of colour and distortion of propagation lines are indicative of non-planar shear wave propagation; these regions also exhibit a higher SD of the mean and a higher mean speed. Figure 3.4 demonstrates a range SD’s obtained: ranging from an SD of 2.1% through to an SD of 38%, with examples of the elastogram and propagation maps and mean speeds obtained.

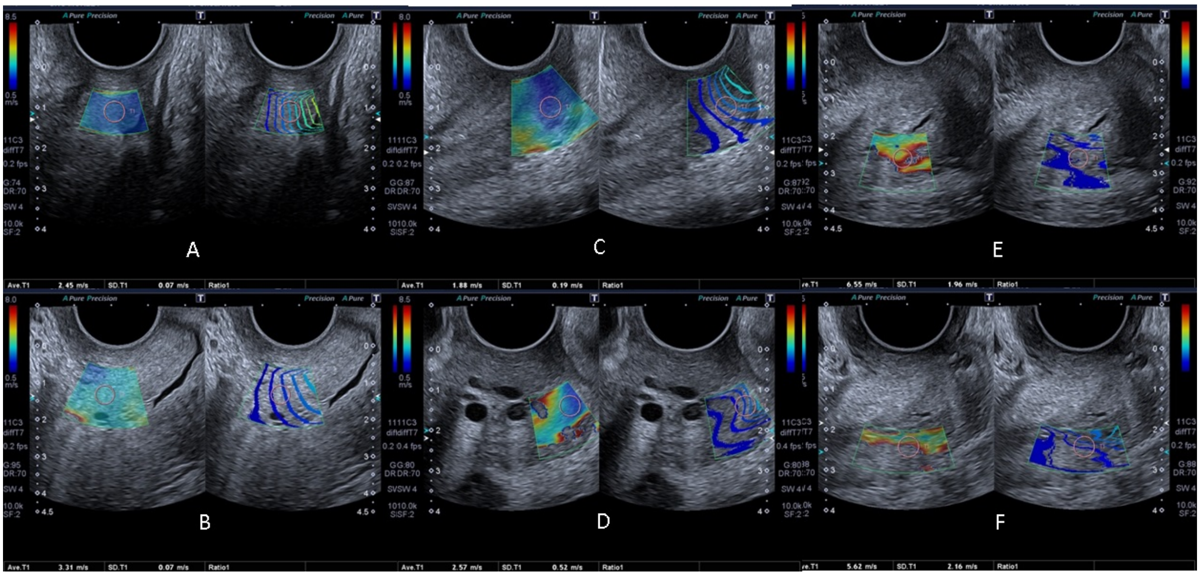


Figure 3.4: Example of changes in distortion of propagation lines and loss of elastogram colour with increasing % of SD of the mean speed:

A- Mean speed 2.45m/s (SD 0.07): 2.8%

B- Mean speed 3.31m/s (SD 0.07): 2.1%

C- Mean speed 1.88m/s (SD 0.19): 10%

D- Mean speed 2.57m/s (SD 0.52): 20%

E- Mean speed 6.55m/s (SD 1.96): 30%

F- Mean speed 5.62m/s (SD 2.16): 38%

The aforementioned factors should be considered when ascertaining the precision of the SWS. The authors considered regions of the elastogram with loss of colour fill and concordant distorted propagation maps and an elevated SD to have non-planar shear wave propagation. These qualitative factors and an SD of greater than 20% of the mean speed (quantified mathematically) was used as a cut off above which mean SWS was considered artifactually increased and not reliable. Unreliable measurements were excluded during statistical analysis.

3.3.2.4 Transducer pressure

The transmission of the main pulse and resultant shear waves can be affected by numerous ultrasound induced artifacts. [24] It is ideal to optimize the B-mode image and obtain an optimal ultrasound window before the application of SWE. [20] Care should be taken to minimise probe pressure on the tissue of interest, whilst maintaining a good B-mode window.[12] A localised pre-stress can result in apparent high SWS values due to non-linear tissue responses.[24]

To assess the magnitude of this effect, we studied if a change in transducer pressure on the cervix alters the resultant shear wave speeds. To this end, ten participants were examined with increased and reduced transducer pressure. All regions of the cervix were interrogated as previously described. The change in distance to the ROI between increased and reduced pressure was as follows: external os anterior 4.3mm (2-10mm), external os posterior 4.2mm (1-9mm), internal os anterior 4.2mm (2-7mm), internal os posterior 4.2mm (1-8mm).

3.3.2.5 Inter-operator testing

Inter-operator testing was performed on 15 participants. For each participant the first sonographer obtained shear wave readings at all 4 regions of interrogation. The secondary sonographer then performed the same set of readings at each of the 4 regions. The mean speed obtained by each sonographer was tested for concordance.

3.3.2.6 Statistical analysis

Descriptive data were presented as mean ± SD. The variables were input to assess normality using a Kolmogorov-Smirnov Test. The data did not differ significantly ($p>0.05$) from normality. A paired samples t-test was used to compare the speed measurements obtained from each region of the cervix. The null hypothesis, H_0 : speed measurements from region 1 = speed measurements from region 2, which is operationalized as the paired differences in speed with a posited mean of zero, was tested against a two-sided alternative, at the 5% level of statistical significance, ($p<0.05$).

Inter-operator agreement compares the speed obtained from each sonographer using an Intra-class Correlation Coefficient (ICC). A low level of agreement being close to 0 and a high level of agreement defined as 1. ICC estimates and their 95% confidence intervals were calculated based on a mean rating (k = 3), absolute agreement, 2-way mixed effects model.[25,26]

Data analysis was performed using SPSS version 26.0 (SPSS V26.0, Chicago, USA).

3.4 **Results**

Seventy three women were considered eligible for this study. Four did not give consent to having the elastography imaging performed due to the extra time required. Sixty nine participants had a mean age of 34 years (range: 18-49 years), with a mean gestation of 1 delivery (range: 0-8 gestations). All measurements returning a SD of greater than 20% of the mean speed were removed. Participants with two or more reliable measurements obtained in each region of the cervix were included in the statistical data set to facilitate a mean speed obtained over more than one measurement. Of the 69 participants 3 were unsuccessful in obtaining any reliable shear wave measurements in all regions due to the cervix being in the vertical position relative to the transducer face.

The number of reliable measurements obtained in each region for the remaining 66 participants, and the mean cervical speed and standard deviation for each region can be seen in Table 3.1. Stiffness results for each region were assessed for differences in concordant pairs as shown in Table 3.2. The number of reliable measurements obtained was assessed dependent on cervical canal position. The number of measurements obtained with differing positions of the uterine cervix, are presented in Table 3, with a diagrammatic representation of the positions presented in Figure 3.5. SWS values for different age ranges, stage of menstrual cycle medical history and ethnicity are presented in Table 3.4. The mean speed measurements obtained with normal and reduced probe pressure are shown in Table 3.5.

Inter-operator testing was performed on 15 participants. The external os anterior and posterior were comparable for 15 participants; the internal os anterior was comparable for 14 participants, with measurements unobtainable in 1 participant for both sonographers. The internal os posterior was comparable for only 6 participants, with shear wave propagation in the remaining 9 participants unobtainable for both sonographers. The ICC obtained at the regions of the cervix was as follows - external os anterior 0.83 (CI 0.45 – 0.95), external os posterior 0.69 (CI 0.07-0.90), internal os anterior 0.92 (CI 0.76 – 0.97), internal os posterior 0.90 (CI 0.37-0.98)

Table 3.1: Summary of shear wave measurements obtained for the uterine cervix

Participants in total-66	Successful measurements obtained (participants)	Mean speed (m/s)	Standard Deviation (SD)	Total number of successful measurements for all participants out of a possible 198
External os Anterior	63	2.52	0.49	184
External os Posterior	55	2.87	0.63	158
Internal os Anterior	55	3.29	0.79	157
Internal os Posterior	26	4.10	1.11	78

Table 3.2: Summary of statistical differences in stiffness between regions of the cervix for all participants

Comparisons	Number of cases compared	Mean difference in speed (m/s) & (SD)	SE of mean	Significance (p=0.05)
External os anterior vs posterior	52	-0.44 (0.69)	0.09	p<0.001
Internal os anterior vs posterior	22	-1.13 (1.11)	0.24	p<0.001
Anterior internal os vs anterior external os	55	0.79 (0.70)	0.09	p<0.001
Posterior internal os vs posterior external os	21	1.42 (0.88)	0.19	p<0.001

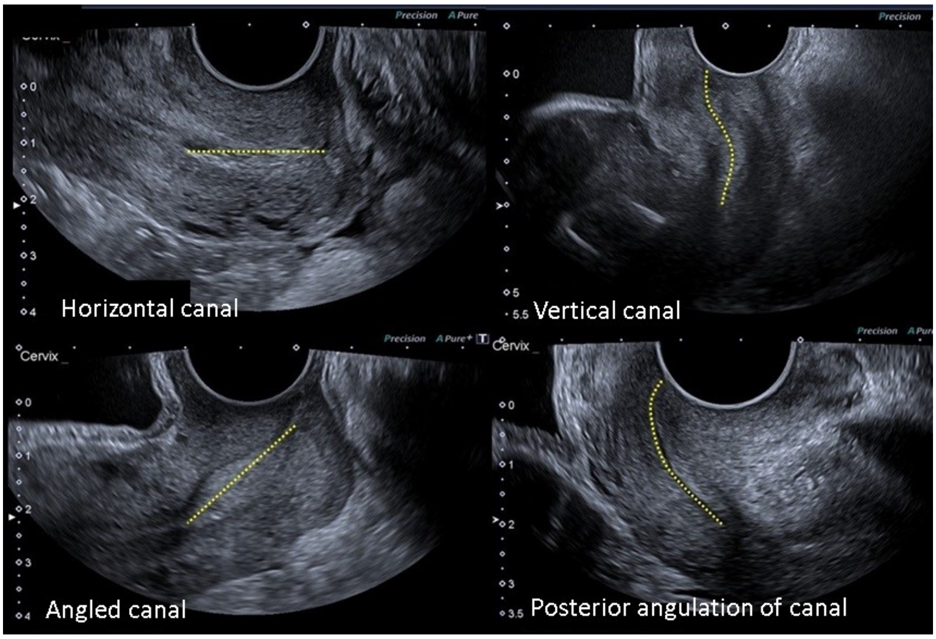


Figure 3.5: Example of anatomical positions of the uterine cervix that correlate to the results in Table 3. Horizontal Canal – cervical canal is approximately 90° to the transducer face. Angled canal – cervical canal increases the angle with the transducer face with the external os being closer to the transducer, and internal os moving superiorly and a great distance from the transducer face. Vertical canal – cervical canal is vertical to the transducer face. Posterior angled canal – cervical canal is at an angle to the transducer face with external os being close to the transducer and the internal os moving posteriorly and a greater distance from the transducer face.

Table 3.3: Summary of number of reliable interrogations registered in each region of the cervix with varying anatomical position

		Number of accurate interrogations in each region			
Cervical Canal Orientation	Total	External Os Anterior	External Os Posterior	Internal Os Anterior	Internal Os Posterior
Horizontal	21	21	17	20	10
Angled	33	33	30	31	11
Vertical	7	7	5	3	3
Posterior angulation	2	1	2	1	1

Table 3.4: Summary of mean speed obtained in each region dependent on patient characteristics

		Mean speed in m/s and (SD) for regions of the cervix			
Participant characteristics	Number of participants	External Os Anterior	External Os Posterior	Internal Os Anterior	Internal Os Posterior
Age range 18-25	13	2.27 (0.33)	2.61 (0.63)	3.19 (0.77)	3.67 (0.15)
Age range 26-33	16	2.47 (0.42)	2.86 (0.59)	3.02 (0.49)	4.15 (0.98)
Age range 34-41	19	2.49 (0.46)	2.96 (0.61)	3.17 (0.37)	4.10 (1.37)
Age range 42-49	18	2.77 (0.58)	2.95 (0.72)	3.66 (1.11)	4.22 (1.34)
Early Proliferative	15	2.60 (0.52)	3.04 (0.37)	3.29 (1.23)	4.87 (1.37)
Late Proliferative	24	2.39 (0.48)	2.88 (0.72)	3.22 (0.61)	4.03 (1.40)
Early Secretory	23	2.57 (0.47)	2.84 (0.66)	3.31 (0.61)	3.69 (0.49)
Late Secretory	4	2.85 (0.62)	2.46 (0.51)	4.48	4.61
Nulliparous	22	2.39 (0.47)	2.71 (0.52)	3.20 (0.59)	3.90 (0.47)
Primiparous	16	2.63 (0.41)	2.82 (0.56)	3.13 (0.58)	4.26 (0.88)
Multiparous	28	2.56 (0.53)	3.00 (0.73)	3.45 (1.01)	4.13 (1.50)
Vaginal deliveries	27	2.64 (0.477)	2.82 (0.66)	3.56 (0.95)	4.46 (1.24)
C-section	13	2.45 (0.54)	3.03 (0.53)	2.89 (0.43)	3.90 (1.51)
European	46	2.54 (0.51)	2.94 (0.66)	3.41 (0.82)	4.07 (1.10)
Asian	15	2.51 (0.39)	2.74 (0.59)	3.09 (0.53)	4.47 (0.71)
Middle Eastern/Indian/African	5	2.39 (0.50)	2.92 (0.64)	2.39 (0.87)	4.04 (1.10)

Table 3.5: Comparison of shear wave speeds and (SD) obtained with reduced probe pressure and pressure on anterior fornix increased to a level appropriate for B-mode imaging

	External Os Anterior	External Os Posterior	Internal Os Anterior	Internal Os Posterior
Reduced probe pressure	2.42m/s (0.52)	2.64m/s (0.57)	3.36m/s (0.51)	4.62m/s (1.18)
Increased probe pressure	4.89m/s (1.79)	5.13m/s (1.91)	5.23m/s (2.04)	5.26m/s (0.65)

3.5 **Discussion**

The cervix creates a challenge in the accurate use of SWE to assess its stiffness. Spatial variations of cervical tissue composition and structure can complicate shear wave propagation. Transducer positioning is limited to the anterior fornix adjacent to the external os with transducer angulation required to interrogate the internal os. As our results show, reliable shear wave production is more likely to be produced anteriorly in the cervix, with a greater number of reliable speeds obtained at the external os than the internal os. The internal os posteriorly is most likely to produce inaccurate or a loss of shear wave propagation in all anatomical positions, with depth of interrogation appearing to be problematic in some patients.

The research by Peralta et al[15] used SWE to measure elasticity of the external os and mid cervix. This research used 6mm ROIs at the external os, with the mid cervix measurements placed at a close distance from these. In this study of 40 participants mid cervix anterior and posterior measurements were not obtainable in one and two participants, respectively.[15] Our results showed a greater proportion of unsuccessful SWE measurements at the internal os. Depending on cervical position the posterior portion of the internal os in particular can reach a depth greater than 3cm from the transducer face (Figure 3.6). A recommendation from Canon Medical (Otawara-shi, Tochigi, Japan) is that utilising the endocavity transducer as described previously; the main push pulses can be expected to produce shear waves to a depth of 3cm using an ultrasound phantom with an acoustic attenuation of 0.5 dB cm^{-1} MHz^{-1}. The cervix has a high acoustic attenuation of over double that of the liver at 1.3 to 2.0 dB $cm^{-1}MHz^{-1}$. [6] This increased attenuation decreases the penetration depth of the main push pulse, and reduces its ability to generate measurable tissue displacements.[6] The challenges for SWS estimates of the cervix with an endovaginal transducer may relate to its depth-dependent signal-to-noise ratio, in tissues it is relative to the focal depth of the transducer, and thus the regions that are deep and proximal in the cervix can be difficult to access with the main pulse.[6]

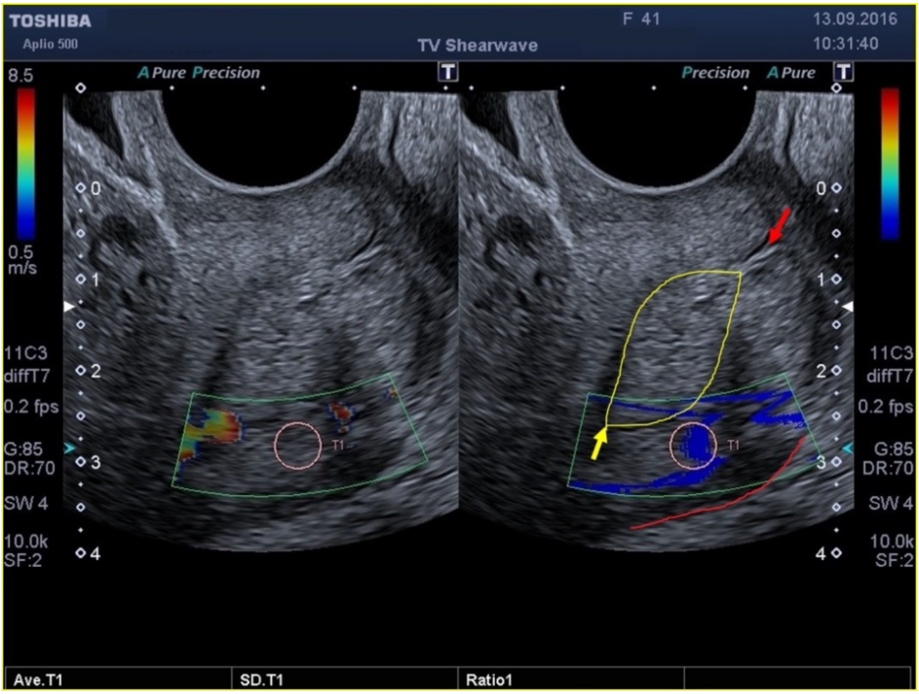


Figure 3.6: SWE of the internal os posterior with a ROI placed at a depth of 3cm, resulting in a non-registration of SWE measurements. The red arrow is pointing to the external os, yellow to internal os and the endocervical mucosa and posterior margin of the cervix has been outlined in yellow and red respectively.

Too much transducer pressure can produce a pre-stress load,[24] that can falsely elevate shear wave speeds. As shown in Table 3.5, increased probe pressure caused an increase in resultant shear wave speeds both anteriorly and posteriorly in the cervix. It was noted that on two participants the increase in pressure resulted in an improvement in shear wave propagation posterior to the cervical canal, but in most participants the pre-stress was transferred to both the anterior and posterior cervical tissues. Of note was that when the increased transducer pressure was applied the SD of the mean speed also increased. Figure 3.7 is an example of the change in SWE speed obtained with gentle and then increased probe pressure. The transvaginal approach can be problematic as a small amount of transducer pressure is required to make contact with the anterior fornix to acquire a good B-mode window prior to the application of the SWE. The transducer can be withdrawn to release this pressure but a level of contact is still required. We conclude that pre-compression can alter the SWS estimation in the cervix and that non-linear tissue responses or mechanical compression of the collagen layers by the transducer may be possible causes.

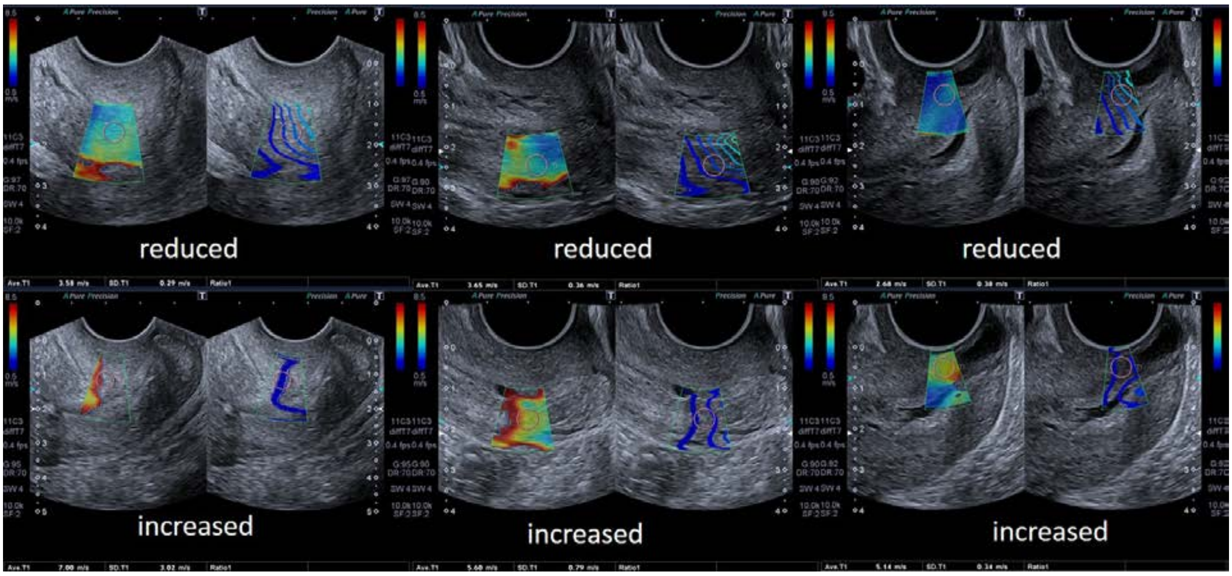


Figure 3.7: SWE elastography demonstrating changes in shear wave speeds obtained with gentle and increased probe pressure in the internal os anterior and posterior and external os anterior.

As shown in Table 3.4 there appears to be minimal difference in SWS between nulliparous and parous patients. There were similar speeds obtained for women with vaginal deliveries and c-section deliveries and also similar speeds between ethnicities. It also appears that mostly there is an overall increase in cervical stiffness with age, and that SWE speed at the internal and external os may alter at different stages of the menstrual cycle. The cervix has been shown to alter its width and length throughout the menstrual cycle. The sphincter-like effect of the collagenous and muscular fibres at the internal os has its greatest strength during the luteal phase of ovulation and relaxes up to two days prior to menstruation.[21] Our results showed the greatest speeds at the internal os were obtained during the secretory phase of the endometrium, corresponding to the luteal ovarian phase. Further research could incorporate shear wave speeds obtained during the first few days of menstruation when the internal os should be at its softest. Larger numbers from each group would be needed to draw robust conclusions.

The internal os showed a significant increase in speed compared to external os both anteriorly and posteriorly. The research by Carlson et al[23] also demonstrated this phenomenon with greater differences in shear wave speed between the external and internal os on the unripen cervix specimens versus the specimens that had been chemically ripened.

Research on the use of strain elastography on the maternal cervix for the prediction of preterm birth documented no appreciable difference in cervical stiffness between the anterior and posterior cervix,[27] whilst the study by Molina et al[10] showed a reduced stiffness in strain values in the posterior cervix. As reported by Hernandez et al[13] and Peralta et al[15], our results also show that the posterior part of the cervix appears to register a higher speed than the anterior part in this cohort, with greater differences registered at the internal than the external os. As can be seen in Figure 3.2, when obtainable, the arrival time of the shear wave appears to be faster in the posterior cervix with widening of the propagation lines posteriorly compared to anteriorly. There was also a greater divergence from parallel of the propagation lines deep to the endocervical mucosa and canal in the posterior cervix, with less measurements being obtainable in this region. Carlson et al[23] utilised hysterectomy specimens of the cervix to obtain shear wave speeds. The specimen was dissected and a 9MHz linear array transducer was used to take measurements from the canal surface of the specimen. This research found a small difference between anterior and posterior shear wave speeds in the unripen cervix, with average speeds formulated of 3.45±0.97m/s and 3.56±0.92m/s respectively. Larger differences were observed in ripened specimens. Our results show a larger difference in speeds obtained between the anterior and posterior cervix at the internal os with a similar difference as Carlson et al[23] at the external os.

The cervical canal could be considered a shear wave boundary, surrounded by aligned collagen fibre bundles as previously described.[23] The appendix to the EFSUMB Guidelines and Recommendations[12] states that boundaries between tissues may reduce or prevent shear wave penetration across the boundary. Shear wave scattering, reflection and refraction artifacts can also be caused by variations in tissue density which may result in errors in shear wave estimation.[12] Material anisotropy can alter resultant shear wave speed.[12] In patients with an axial position ranging from mild to fully axial, the main pulse may be approaching the collagen fibres at an angle that may cause anisotropy of the muscular collagen layer. Reducing the elastogram box size improved the interrogation of the axial cervix, however in the axial position the internal os is difficult to interrogate in most cases. We hypothesise that this anisotropy may be causing artifactual increases in shear wave speed deep to the cervical canal or a loss of effective shear wave propagation.

The internal os anterior showed a good level of agreement between sonographers, as did the internal os posterior and external os anterior, though these regions had a broader confidence interval reducing the reliability of the result. The external os posterior showed poor to moderate agreement with a wide confidence interval obtained for the ICC in this region.

This research concludes that the attenuation properties of the cervix and shear wave artifacts are reducing the production of, and precision of, shear wave measurements obtained deep to the cervical canal. It is important to reduce transducer pressure to the anterior fornix to minimise the pre-stress that may cause an increase in shear wave speeds in both the anterior and posterior cervix. The anterior cervix is more likely to produce more precise shear wave values than the posterior cervix, with the anatomical position of the cervix appearing to affect the success of resultant shear wave measurements, with the ideal position being a canal that is horizontal in position.

3.6 **References**

1. Myers K M, Feltovich H, Mazza E et al. The mechanical role of the cervix in pregnancy. *J Biomech* 2015; 48(9): 1511-1523.

2. Retzke JD, Sonek JD, Lehmann J, Yazdi B, Kagan KO. Comparison of three methods of cervical measurement in the first trimester: Single-line, two-line, and tracing. *Prenat Diagn* 2013; 33(3):262-268.

3. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol* 2012; 206(2):124.e1-124.e19.

4. Larma JD, Iams JD. Is sonographic assessment of the cervix necessary and helpful? *Clin Obstet Gynecol* 2012; 55(1):324-335.

5. Olson Chen C. Ultrasound for cervical length. *Ultrasound Clin*. 2013; 8(1):1-11.

6. Palmeri M, Feltovich H, Homyk A, Carlson L, Hall T. Evaluating the feasibility of acoustic radiation force impulse shear wave elasticity imaging of the uterine cervix with an intracavity array: a simulation study. *IEEE Trans Ultrason Ferroelectr Freq Control* 2013; 60(10):2053-2064.

7. House M, Socrate S. The cervix as a biomechanical structure. *Ultrasound Obstet Gynecol* 2006; 28(6):745-749.

8. Wozniak S, Czuczwar P, Szkodziak P, et al. Elastography in predicting preterm delivery in asymptomatic, low-risk women: a prospective observational study. *BMC Pregnancy and Childbirth* 2014; 14:238.

9. Preis K, Swiatkowska-Freund M, Pankrac Z. Elastography in the examination of the uterine cervix before labour induction. *Ginekol Pol* 2010;81: 757-761.

10. Molina FS, Gómez LF, Florido J, Padilla MC, Nicolaides KH. Quantification of cervical elastography: a reproducibility study. *Ultrasound Obstet Gynecol* 2012; 39:685-689.

11. Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. *J Acoust Soc Am* 2001; 110:625-634.

12. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. *Ultraschall Med* 2013; 34(2):169-84.

13. Hernandez-Andrade E, Hassan SS, Ahn H, et al. Evaluation of cervical stiffness during pregnancy using semiquantitative ultrasound elastography. *Ultrasound Obstet Gynecol* 2013; 41:152-161.

14. Muller M, Aït-Belkacem D, Hessabi M, et al. Assessment of the Cervix in Pregnant Women Using Shear Wave Elastography: A Feasibility Study. *Ultrasound Med Biol* 2015; 41(11):2789-2797.

15. Peralta L, Molina FS, Melchor J, et al. Transient Elastography to Assess the Cervical Ripening during Pregnancy: A Preliminary Study. *Ultraschall Med* 2017; 38(04):395-402.

16. Carlson LC, Romero ST, Palmeri ML, et al. Changes in shear wave speed pre- and post-induction of labour: a feasibility study. *Ultrasound Obstet Gynecol* 2015; 46(1):93-98.

17. Bakay OA, Golovko TS. Use of elastography for cervical cancer diagnostics. *Exp Oncol* 2015; 37(2):139-145.

18. Eng J. Sample Size Estimation: How Many Individuals Should Be Studied? *Radiology* 2003; 227(2):309-313.

19. Thiele M, Detlefsen S, Sevelsted Moller L, et al. Transient and 2-Dimensional Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver Fibrosis and Cirrhosis. *Gastroenterology* 2016; 150(1):123-33.

20. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). *Ultraschall Med* 2017;38:e16-e47.

21. Nott JP, Bonney EA, Pickering JD, Simpson NAB. The structure and function of the cervix during pregnancy. *Transl Res Anatomy* 2016; 2:1-7.

22. Vink JY, Qin S, Brock CO, et al. A new paradigm for the role of smooth muscle cells in the human cervix. *Am J Obstet Gynecol* 2016; 215(4):478.e1.

23. Carlson LC, Feltovich H, Palmeri ML, Rio AMd, Hall TJ. Statistical analysis of shear wave speed in the uterine cervix. *IEEE Trans Ultrason Ferroelectr Freq Control* 2014; 61(10):1651-1660.

24. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. *Ultrasound Med Biol* 2015; 41(5):1126-47.

25. Fleiss JL, Cohen J. The Equivalence of Weighted Kappa and the Intraclass Correlation Coefficient as Measures of Reliability. *Educ Psychol Measurement* 1973; 33(3):613-619.

26. Rankin G, Stokes M. Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. *Clin Rehabil* 1998; 12(3):187-199.

27. Swiatkowska-Freund M, Preis K. Elastography of the uterine cervix: implications for success of induction of labour. *Ultrasound Obstet Gynecol* 2011; 38:52-56.

Chapter 4

Shear wave elastography of the maternal cervix:

A transabdominal technique

4.1 Abstract

Objectives: Reduced cervical length as seen on transvaginal ultrasound is a strong indicator of spontaneous preterm birth in women at high risk of preterm birth. In low risk women the appropriate method to assess this risk is still debatable. Ultrasound elastography has been used to assess cervical softening. This research aimed to assess the accuracy of shear wave speeds obtained deep to echo free fluid filled structures, and the use of 2DSWE on the maternal cervix using a transabdominal ultrasound approach.

***Methods*:** Shear wave speed measurements were obtained in the anterior and posterior portions of the internal and external cervical os on 50 gravid participants in the mid-trimester, with a partially full maternal bladder. Agreement of shear wave speed measurements obtained through fluid and directly onto an ultrasound phantom was also assessed for accuracy of shear wave speeds obtained in the phantom through echo free fluid compared to with the transducer directly on the phantom.

Results: There was no difference in shear wave speeds obtained in the phantom with either direct contact or through the saline water-bath ($p<0.05$). In 50 participants, measurements were obtainable at the external os anterior and posterior in 49 and 38 participants and in 47 and 42 participants for internal os anterior and posterior. The mean speed obtained at the external os anterior and posterior, was 2.01 ± 0.51m/s and 2.38 ± 0.47m/s respectively, and at the internal os anterior and posterior, 2.49 ± 0.50m/s and 2.58 ± 0.41m/s.

Conclusion: Shear wave speed measurements can be obtained in the maternal cervix using a TA approach with a moderately full maternal bladder in most patients, with a larger number

of accurate shear wave measurements obtained in the anterior cervix compared to the posterior.

Key words Shear wave, elastography, cervix, preterm birth, ultrasound

4.2 **Introduction**

Ultrasound shear wave elastography (SWE) is a relatively new technique that can produce a quantifiable measurement of stiffness of tissues in-vivo. SWE utilises a modified sound wave to produce shear waves within tissues.[1] Faster shear wave speeds are produced in stiffer tissues, with slower speeds being recorded in softer tissues.[2]

Preterm birth continues to have significant implications for the risk of neonatal mortality and morbidity,[3] with the preterm birth rate being 7.5% in Australia in 2011.[4] A shortened maternal cervix as measured by transvaginal ultrasound has been shown to be a strong indicator of subsequent spontaneous preterm birth (SPTB).[5] Even so, a shortened cervical length has a low sensitivity for SPTB in the low risk population.[6, 7] Elastographic assessment of cervical strength may have the potential to predict cervical insufficiency with greater accuracy than length alone.[2] It may be possible to identify women who are at increased risk of PTB due to cervical softening that occurs before a reduction in cervical length with strain elastography, but this method lacks standardisation between sonographers.[8, 9] SWE is advantageous as it provides a quantitative evaluation of the speed of propagation of the shear wave in tissues with less sonographer dependance.[10, 11]

Research utilising an intracavity transducer and the transvaginal ultrasound approach using SWE has shown that it may be possible to identify a reduction in shear wave speed indicating cervical softening, prior to a reduction in cervical length.[8, 11] It has also been found that some patients will decline the transvaginal approach and that problems with language barriers can also impede consent.[12, 13] The cervix is has viscoelastic tissue properties that may alter during pregnancy,[14] and with preterm cervical insufficiency. This research assesses the use of a transabdominal (TA) ultrasound approach with a partially full maternal bladder to acquire shear wave speeds on the maternal cervix.

The Canon Aplio 500 system utilises a two dimensional shear wave technology (2DSWE). 2DSWE utilises a B-mode image that is overlayed by the elastogram in real time. Ultrasound pulses are modified to a high intensity to produce shear waves in the region of interest. Shear waves cannot be produced in fluid, but it has been shown that it may be possible to obtain accurate shear wave measurements deep to echo free fluid filled structures.[15] This research also assesses if shear wave speeds obtained with direct transducer contact onto an ultrasound phantom are the same as if the transducer is placed on a fluid filled stand-off.

4.3 Materials and Methods

4.3.1 Subject recruitment

This study was conducted at branches of SKG Radiology in Perth, Western Australia. A prospective study of women presenting for their routine second trimester fetal morphology ultrasound was performed. All participants were over 18 year of age with varying pregnancy history and ethnicity and body habitus. All participants were required to read an information sheet and give informed consent to be enrolled into the study. Exclusions were women with a multiple gestation or women already receiving vaginal progesterone or with current cervical cerclage placement. Patients unable to give informed consent due to language barriers were also excluded. Ethics approval was granted from the clinical site and Curtin University Human Research Ethics Committee. This study presents the first 50 cases obtained as part of a larger research design, and presents the use of a new technique utilising two dimensional shear wave to obtain shear wave speed measurements on the maternal cervix using a transabdominal approach.

4.3.2 Study design

All imaging was performed on the Canon Aplio 500 version 6 ultrasound machine (Otawara-shi, Tochigi, Japan), using the 6C1 curvilinear transducer. The elastogram was set to a size of 20 x 20mm with the region of interest (ROI) set to a 5mm sphere for the maternal cervix. The elastogram opacity was set to 0.6. Transducer shear wave frequency was 2.2MHz with a tracking frequency of 0, equating to a 2.2MHz push pulse and 2.2MHz tracking pulse. A 'continuous' mode cine-loop of frames of greater than three seconds of stable elastogram was stored at each region,[16] with a frame rate setting of 1, equating to 0.4fps. All data was collected by a single sonographer with over 20 years' experience in the field of sonography. Intra-operator testing was performed on 20 of the participants. Shear wave speed measurements obtained in each region were compared for repeatability by the single sonographer.

4.3.3 Phantom testing

The Elastography Quality Assurance (QA) Phantom (CIRS, Norfolk, VA, USA) with a background speed of 2.94m/s and lesion speed of 1.91/s was used for this experiment. This phantom was used to enable testing of the specified lesion speed with both direct transducer contact and through the saline standoff. The lesion is located at a depth of 3cm and the ROI was set to a 20mm sphere to encompass the lesion. The transducer was supported independently with a transducer clamp and stand as shown in Figure 4.1. Acoustic ultrasound gel was used to facilitate transducer contact. Shear wave speed (SWS) measurements were acquired with the transducer in direct contact with the phantom and through a saline stand-off with a depth of 4.5cm. The saline standoff is intended to mimic the urinary bladder and to this end normal saline was utilised with an osmolality of 300mOsm/kg, similar to that of urine.[17] Other factors remained stable as above.

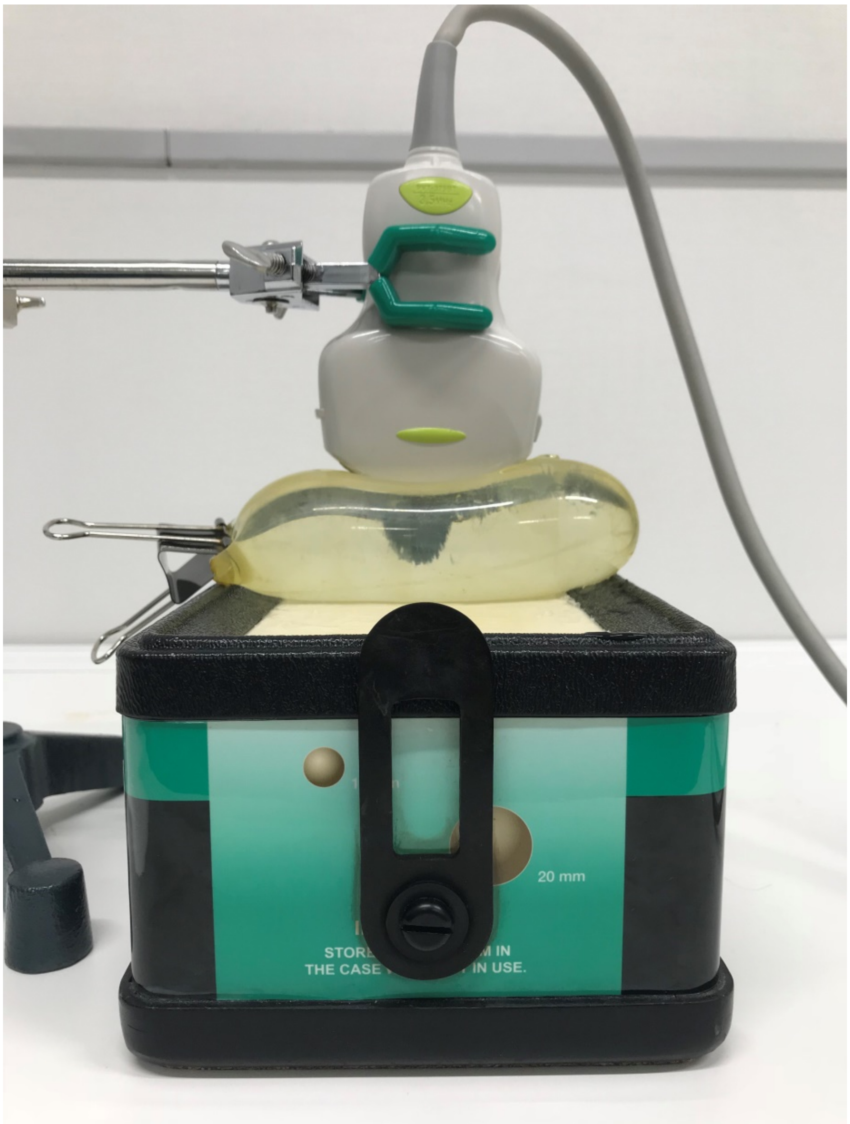


Figure 4.1: Image of transducer placement during SWS acquisitions using the Elastography QA Phantom with the saline standoff. Clamp and stand support of the transducer is also demonstrated.

4.3.4 Imaging methodology

The maternal bladder was partially filled to a minimum required volume to provide a B-mode window for visualisation of the cervix and to allow adequate through transmission to achieve transmission of the SWE main pulse to the cervix. The total bladder volume was variable dependant on individual participant anatomical characteristics, with bladder filling adequate to allow the superior to inferior dimension of the bladder to cover the length of the cervical canal as demonstrated in Figures 4.2 and 4.6. The patient is placed in the supine position with transducer placement inferiorly in the midline just superior to the symphysis pubis. Measurements were acquired in the mid-sagittal plane of the cervix. The cervical canal, internal and external os were identified.[18] Transducer orientation was aligned to the length of the cervical canal and tilted to as close to a perpendicular approach to the canal as technically possible. Increasing transducer pressure has been shown to cause compression of tissues that can an increase in SWS, particularly in superficial tissues.[19] In this study transducer pressure was kept to a minimum. The 5mm ROI was positioned adjacent to the endocervical canal and mucosa, and central to the outer serosal layer, in the circumferential layer of smooth muscle and collagen thought responsible for cervical dilatation.[20] Shear wave speed measurements were obtained at the internal and external os, anterior and posterior portions as can be seen in Figures 4.2 A-D. The mean speed was recorded three times in each anatomical location.

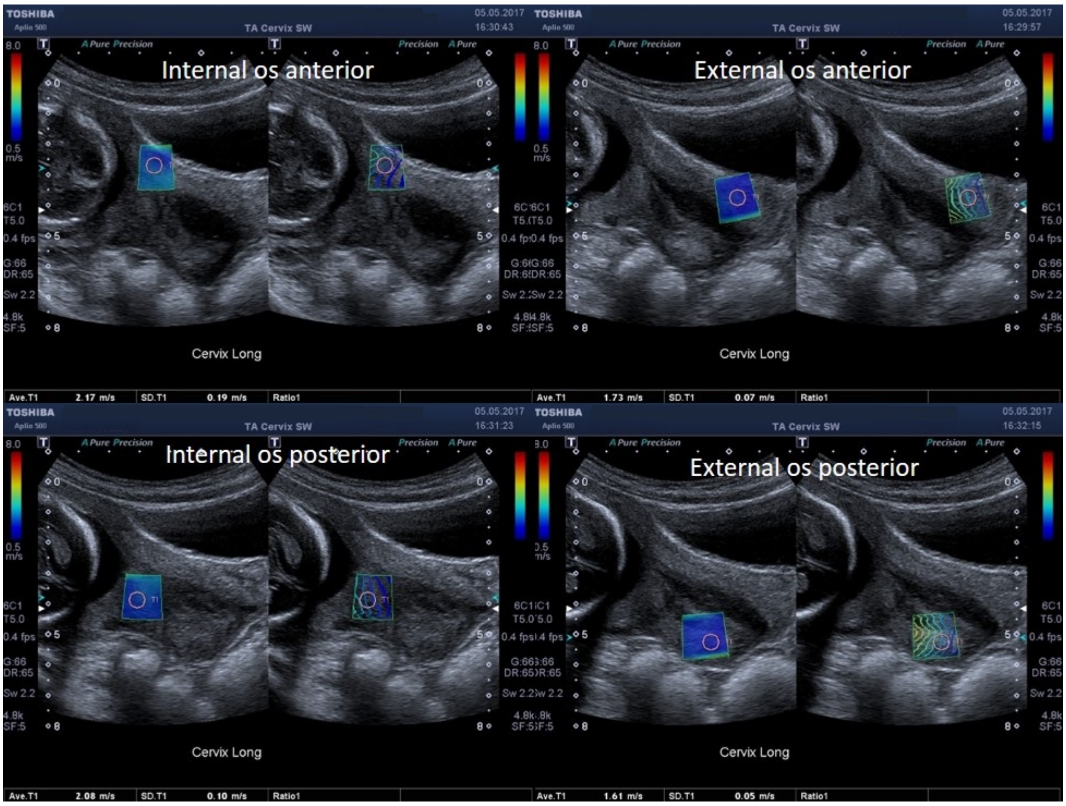


Figure 4.2: A-D Example of elastogram and ROI placement in the anterior and posterior portions of the internal and external os. Shear wave speed obtained at the internal os anterior and posteriorly is 2.17 ± 0.19m/s and 2.16 ± 0.12m/s. Shear wave speed obtained at the external os anteriorly and posteriorly were 1.73 ± 0.07m/s and 1.72 ±0.06m/s respectively.

4.3.5 Shear wave speed accuracy

The main pulse used in shear wave elastography and the propagation of the shear waves can be affected by ultrasound artifacts.[19] The Canon Aplio 500 SWE device gives indications of accuracy of shear wave propagation. The ROI registers many hundreds of shear wave speed values simultaneously and the mean speed and one SD is recorded. ROI placement is aided by the use of the elastogram and propagation maps. The regions of most homogenous colour in the elastogram and the most parallel and equidistant lines on the propagation map are indicative of consistent shear wave propagation and will return the lowest SD. Regions with in-homogenous or loss of colour fill in the elastogram and erratic lines in the propagation map are indicative of inconsistent shear wave propagation and will return a high SD. The high SD is indicative of a large variation in SWS obtained within the ROI, and measurements obtained with a high SD usually exhibit a higher mean speed than those obtained in the same region with a lower SD.

SWS measurements were obtained at the anterior and posterior portions of the internal and external os in all 50 participants. Regions exhibiting an in-homogenous or a non-filled elastogram and erratic propagation lines and an SD of greater than 20% of the mean were considered to be indicative of inaccurate shear wave propagation. Inaccurate measurements were excluded from the data set prior to statistical analysis.

The elastogram also gives indications of increased transducer pressure, which can be identified by a red band of colour in the elastogram near field. All imaging was taken with minimal transducer pressure and devoid of the red band.

4.3.6 Safety considerations

It has been recommended that SWE be used with the same safety considerations as Doppler ultrasound,[19] and recommendations have been made for further investigations into the effects of SWE technology on the fetus.[21] Though Doppler technology has become standard practice for fetal examinations, for this study the elastogram was not placed on or closely adjacent to any fetal parts and use of SWE is kept to a minimum. The moderately full bladder was advantageous in that the fetus was displaced cephalad from the maternal cervix.

4.3.7 Statistical analysis

Descriptive data has been presented using the mean ± standard deviation (SD). The variables were assessed using a Kolmogorov-Smirnov Test. The data did not differ significantly (p>0.05) from normality. The speed measurements acquired at each region of the cervix and for phantom testing were compared using a paired samples t-test. The null hypothesis used as follows, H_0 : speed measurements from region 1 = speed measurements from region 2, is formulated as the paired differences in speed with a theorised mean of zero, tested at a 5% level of statistical significance, ($p<0.05$).

Intra-operator agreement was assessed with the null hypothesis, H_0 : mean bias between repeated measurements = 0 using a one sided t-test. Testing incorporated a 5% level of statistical significance ($p<0.05$).

SPSS version 26.0 (SPSS V26.0, Chicago, USA) was used to analyse data.

4.4 Results

Fifty women participated in the early findings over a 7 month period commencing in November 2016. All participants were between 17 and 28 weeks of gestation. The mean age was 28 years (19-43 years). Varying gestational status was included with a mean gestation of 2 (0-9 gestations) and 1 prior delivery (1-3 deliveries). All SWS measurements obtained exhibiting a non-uniform elastogram and propagation map and an SD of greater than 20% of the mean speed were excluded as previously described. A minimum of 2 reliable measurements was required to formulate the mean speed obtained at each region of the cervix. Results incorporating the number of reliable measurements obtained and the mean speed for each region of the cervix are shown in Table 4.1, with Table 4.2 outlining the results of the paired t-test comparing the mean speed obtained at each region of the cervix.

Table 4.1: Number of reliable measurements and mean speeds obtained in each region of the maternal cervix

	Reliable measurements obtained out of the 50 participants	**Mean speed (m/s)**	**Standard Deviation (SD)**	**Number of reliable measurements out of a possible 150**
External os Anterior	49	2.01	0.51	144
External os Posterior	38	2.38	0.47	115
Internal os Anterior	47	2.49	0.50	139
Internal os Posterior	42	2.58	0.41	118

Table 4.2: Results of paired t-test comparing different regions of the maternal cervix

Comparisons	**Number of cases compared**	**Mean difference in speed (m/s) & (SD)**	**SE of mean**	**t(df)**	**Significan ce (*p*=0.05)**	**Statistically significant difference**
External os anterior vs posterior	38	-0.46 (0.45)	0.07	-6.33(37)	.001	Yes
Internal os anterior vs posterior	41	-0.10 (0.56)	0.09	-1.18(40)	.243	No
Anterior internal os vs external os	44	0.48 (0.39)	0.06	8.01(43)	.001	Yes
Posterior internal os vs external os	36	0.188 (0.19)	0.51	2.20(35)	.035	Yes

SD – Standard Deviation

4.4.1 Intra-operator testing

Intra-operator testing was performed on 20 participants. Differences were not statistically different in all regions. The mean difference at external os anterior and posterior was 0.002 ± 0.03m/s (p=0.789) and 0.010 ± 0.06m/s (p=0.505) respectively. The mean difference at internal os anterior and posterior was 0.003 ± 0.04m/s (p=0.735) and -0.004 ± 0.04m/s (p=0.592) respectively.

4.4.2 Phantom testing

Fifteen SWS measurements were obtained in the phantom lesion with both direct transducer contact (Figure 4.3) and through the saline standoff (Figure 4.4), with a saline depth of 4.5cm. The mean speeds obtained in the lesion with direct contact and through the standoff were 1.94 ± 0.04m/s and 1.96m/s ± 0.01m/s respectively. The mean difference between SWS with saline standoff and direct contact being -0.01(SE 0.01); t(15) = -1.26 *p*=0.229.

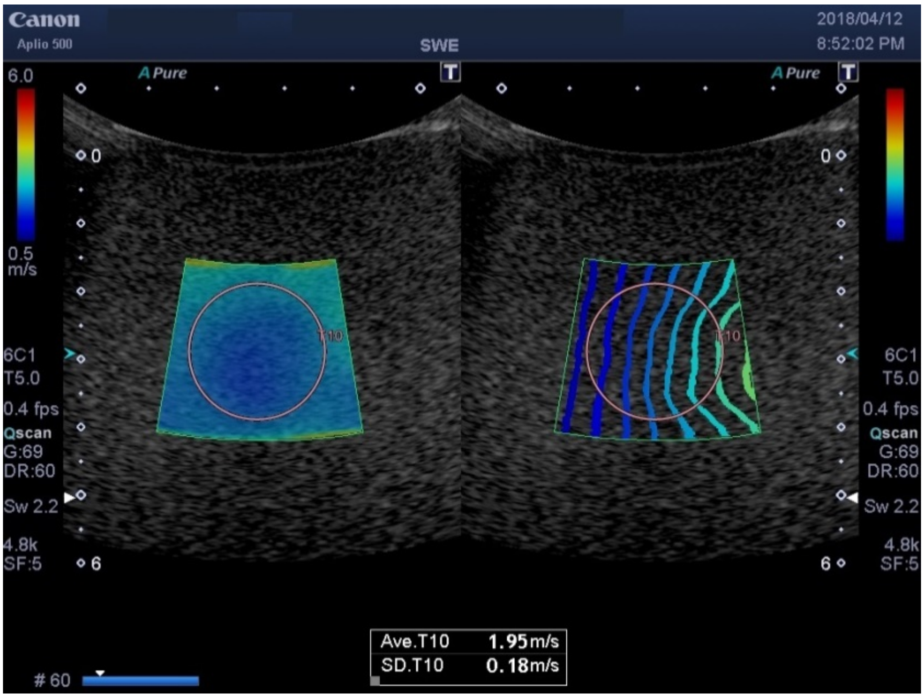


Figure 4.3: Shear wave speed measurement obtained at the level of interest in the Elastography QA phantom with direct transducer contact. Mean speed of 1.95m/s ± 0.18ms.

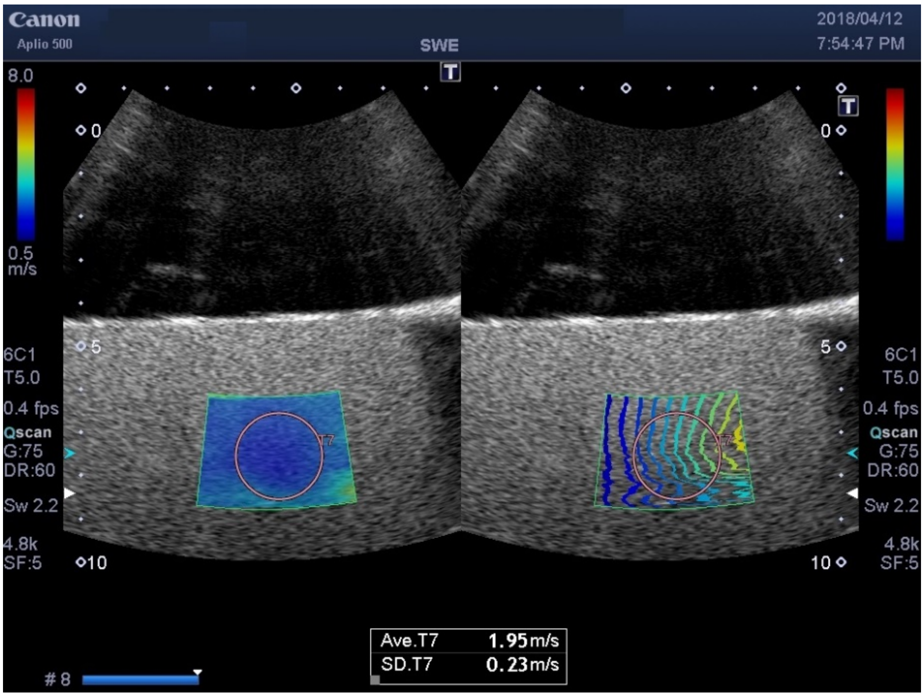


Figure 4.4: Shear wave speed measurement obtained at the level of interest in the Elastography QA phantom with saline standoff at a depth of 4.5cm. Mean speed of 1.95m/s ± 0.23ms.

4.5 Discussion

SWE utilises a sound beam modified to a high intensity, forming the main pulses that are sent vertically into the region to be interrogated, creating sideways movement of shear waves that are tracked by the ultrasound machine in a similar way to Doppler technology.[19] The main pulse can also be focused to the region of interrogation to improve reliability.[15] As opposed to other SWE devices, 2DSWE is able to be utilised deep to echo free fluid filled structures.[15]

Results of the phantom testing showed a statistically insignificant difference (p=0.229) between SWS obtained in the phantom ROI with the transducer placed directly onto the phantom or with transducer placement on the saline standoff.

In this study the cervix is visualized with a moderately full maternal bladder. As with B-mode imaging the bladder was used as an acoustic window to visualize the maternal cervix deep to this and to also allow transmission of the main pulses used in 2DSWE to the cervix. Though shear waves cannot be produced in fluid filled structures,[10] it is possible to produce shear waves in tissues deep to the fluid filled structure if the elastogram is placed in this region as shown in Figures 4.1 and 4.5.

A recommendation for 2DSWE in the liver is that reliable shear wave propagation can be produced at a depth of up to 7cm from the transducer face.[15] As Figure 4.5 demonstrates it appears possible to produce reliable shear wave propagation at a depth greater than 7cm from the transducer face to the cervix through the maternal bladder. The ROI placement in Figure 4.5 can be seen to as placed a depth of 84.6mm from the transducer face. The depth of the maternal bladder is measured at 61.7mm; and the overall depth of tissue to the ROI is measured at close to 22.9mm.

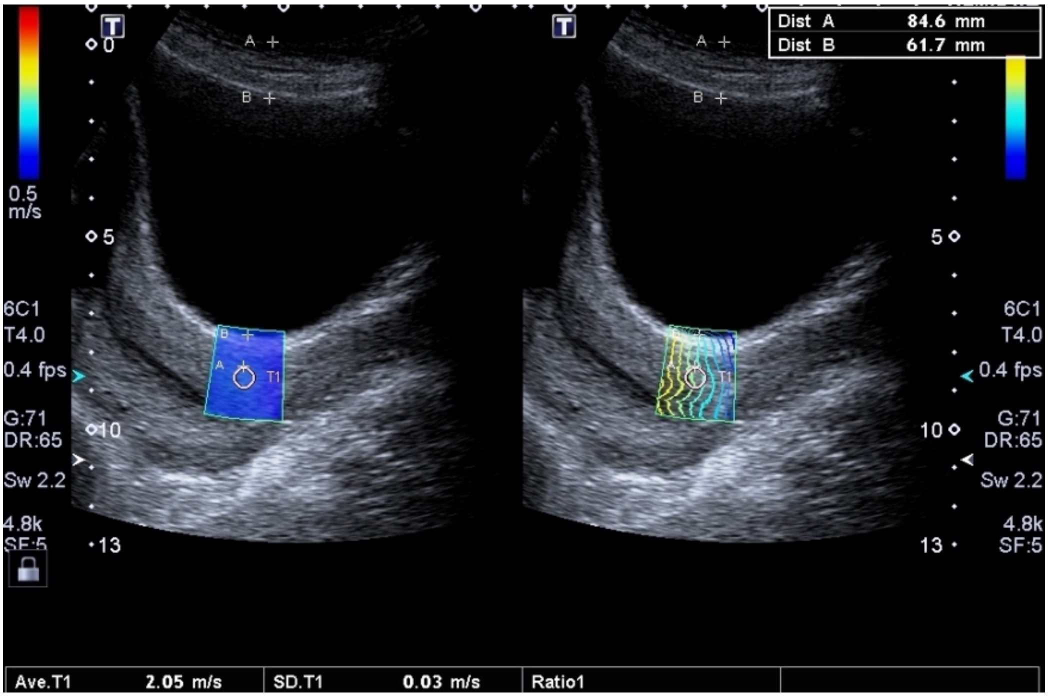


Figure 4.5: Region of interest (ROI) placed at external os anterior with a depth measurement of 84.6mm to the ROI; bladder height is measured to be 61.7mm and the depth of tissues measured at 22.9mm.

For the 50 participants presented in this study, the greatest numbers of reliable SWS speed measurements were obtained at the external os anterior at 49, with 47 measurements obtained at the internal os anterior. The least number of reliable measurements were obtained at the external os posterior at 38, with the internal os posterior achieving 42 reliable SWS measurements.

A greater depth of the main pulse penetration from the transducer face is required to reach the posterior cervix and produce shear wave propagation. As demonstrated in Figures 4.2 and 4.5, the external os posterior is at the greatest depth from the transducer face in most patients, and this is the region that produced the least number of reliable SWS values for this study.

It is an observation from the results of these 50 participants that a cervical canal close to horizontal in orientation so that the internal and external os are a similar distance to the transducer face is the most optimal position to obtain reliable shear wave propagation in all regions. When there is an anterior angulation of the internal os, the internal os is markedly closer to the transducer than the external os and the depth to the external os from the transducer face can be problematic. Increasing depth to all regions of the cervix may be a factor in patients with a large body mass index. A consideration for penetration of the main pulse to the posterior portion of the cervix is the acoustic attenuation properties of the cervix. The cervix has an acoustic attenuation of at 1.3 to 2.0 dB $cm^{-1}MHz^{-1}$ which is over twice the acoustic attenuation of the liver.[3] It would thus be an expectation that the distance of penetration of the main pulse is reduced in the cervix compared to what would be expected in the liver. The cervical canal also has opposing layers of mucosa surrounding a central canal, and it has also been shown that tissue interfaces may be problematic in shear wave elastography.[22]

The results of the research presented in this chapter have shown a statistically significant difference between shear wave speeds obtained in the anterior compared to the posterior external os, with the posterior external os registering a higher mean speed. Interestingly these results showed no statistical difference between the anterior and posterior internal os. Hernandez et al[11] reported an increase in SWS in the cervix posteriorly using a transvaginal ultrasound approach, and Carlson et al[22] used a linear array transducer to measure SWS on chemically ripened and unripened specimens of the cervix. This study reported a small difference in SWS obtained between the anterior and posterior cervix, with greater speeds obtained in the posterior portion, with these differences being greater in the ripened specimens.[22] Using a transvaginal ultrasound approach Peralta et al [23] also found increased stiffness in the posterior cervix using SWE and research into the use of strain elastography has shown no difference or reduced stiffness posteriorly in the cervix.[8, 24] As reported by Carlson et al [22] and Peralta et al [23] the results of this research have also shown an increase in shear wave speeds obtained at the internal os compared to the external os, both anteriorly and posteriorly.

The one experienced sonographer in this study showed good reproducibility of SWS in each region of the cervix, but this study is limited by the data collection being performed by one sonographer. A recommendation would be that this technique is now disseminated to other sonographers with varying levels of experience and inter-operator testing be performed to assess the reproducibility of the technique.

4.6 **Conclusion**

Results of this research show that it is possible to measure shear wave speed in the maternal cervix using a transabdominal approach. A larger number of accurate shear wave measurements can be obtained in the anterior cervix compared to the posterior, with greater shear wave speeds obtained at the internal os compared to external os. Further assessment of shear wave speeds obtained in the maternal cervix may be useful for the identification of softening of the cervical tissues and their possible relationship to cervical insufficiency and spontaneous preterm birth. Practical application of this technology could be the use of a non-invasive technique to assess cervical strength in the mid-trimester, with the potential to predict imminent cervical insufficiency and subsequent spontaneous preterm birth with a greater sensitivity than cervical length alone.

4.7 References

1. Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. Journal of the Acoustical Society of America. 2001; 110(1):625-634.

2. House M, Socrate S. The cervix as a biomechanical structure. Ultrasound in Obstetrics and Gynecology. 2006; 28(6):745-749.

3. Palmeri M, Feltovich H, Homyk A, Carlson L, Hall T. Evaluating the feasibility of acoustic radiation force impulse shear wave elasticity imaging of the uterine cervix with an intracavity array: a simulation study. Ultrasonics, Ferroelectrics, and Frequency Control, IEEE Transactions on. 2013; 60(10):2053-2064.

4. Li Z ZR, Hilder L, Sullivan EA Australia's mothers and babies 2011 Canberra: AIHW; 2013.

5. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm

delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol. 2012; 206(2):124.e1-124.e19.

6. Larma JD, Iams JD. Is sonographic assessment of the cervix necessary and helpful? Clinical Obstetrics and Gynecology. 2012; 55(1):324-335.

7. Olson Chen C. Ultrasound for cervical length. Ultrasound clinics. 2013; 8(1):1-11.

8. Molina FS, Gómez LF, Florido J, Padilla MC, Nicolaides KH. Quantification of cervical elastography: a reproducibility study. Ultrasound Obstet Gynecol. 2012; 39 Molina2012.

9. Wozniak S, Czuczwar P, Szkodziak P, et al. Elastography in predicting preterm delivery in asymptomatic, low-risk women: a prospective observational study. BMC Pregnancy and Childbirth [journal article]. 2014; 14(1):238. Wozniak2014.

10. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med. 2013; 34(2):169-84.

11. Hernandez-Andrade E, Hassan SS, Ahn H, et al. Evaluation of cervical stiffness during pregnancy using semiquantitative ultrasound elastography. Ultrasound Obstet Gynecol. 2013; 41 Hernandez-Andrade2013.

12. Orzechowski KM, Boelig RC, Baxter JK, Berghella V. A universal transvaginal cervical length screening program for preterm birth prevention. Obstet Gynecol. 2014; 124(3):520-5.

13. Orzechowski KM, Boelig R, Nicholas SS, Baxter J, Berghella V. Is universal cervical length screening indicated in women with prior term birth? Am J Obstet Gynecol. 2015; 212(2):234.e1-234.e5.

14. Callejas A, Gomez A, Melchor J, et al. Performance Study of a Torsional Wave Sensor and Cervical Tissue Characterization. Sensors (Basel, Switzerland). 2017; 17(9).

15. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). Ultraschall in Med.

16. Thiele M, Detlefsen S, Sevelsted Moller L, et al. Transient and 2-Dimensional Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver Fibrosis and Cirrhosis. Gastroenterology. 2016; 150(1):123-33.

17. Koeppen BM, Stanton BA. 5 - Regulation of Body Fluid Osmolality: Regulation of Water Balance. In: Koeppen BM, Stanton BA, editors. Renal Physiology (Fifth Edition). Philadelphia: Mosby; 2013. p. 73-92.

18. O'Hara S, Zelesco M, Sun Z. A comparison of ultrasonic measurement techniques for the maternal cervix in the second trimester. Australasian Journal of Ultrasound in Medicine. 2015; 18(3):118-123.

19. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. Ultrasound Med Biol. 2015; 41(5):1126-47.

20. Nott JP, Bonney EA, Pickering JD, Simpson NAB. The structure and function of the cervix during pregnancy. Translational Research in Anatomy. 2016; 2:1-7.

21. Massó P, Rus G, Molina FS. Safety of elastography in fetal medicine: preliminary study on hypoacusis. Ultrasound in Obstetrics & Gynecology. 2017; 50(5):660-661.

22. Carlson LC, Feltovich H, Palmeri ML, Rio AMd, Hall TJ. Statistical analysis of shear wave speed in the uterine cervix. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control. 2014; 61(10):1651-1660.

23. Peralta L, Molina FS, Melchor J, et al. Transient Elastography to Assess the Cervical Ripening during Pregnancy: A Preliminary Study. Ultraschall in Med. 2017; 38(04):395-402.

24. Swiatkowska-Freund M, Preis K. Elastography of the uterine cervix: implications for success of induction of labour. Ultrasound Obstet Gynecol. 2011; 38 Swiatkowska-Freund 2011.

Chapter 5

Shear wave elastography of the maternal cervix:

A comparison of transvaginal and transabdominal

ultrasound approaches

5.1 Abstract

Objectives This work aimed to compare the use of shear wave elastography on the maternal cervix with transvaginal and transabdominal ultrasound approaches, to assess differences in shear wave speeds obtained for possible clinical use.

Methods Using both the transvaginal and transabdominal ultrasound approaches, shear wave speed measurements were attempted at the anterior and posterior portions of the internal and external cervical os on 37 gravid participants. The transabdominal and transvaginal transducers were tested for agreement of shear wave speeds obtained using a quality assurance phantom.

Results A greater number of reliable shear wave speed measurements were obtained in the anterior portion of the cervix in both ultrasound approaches. The mean difference in shear wave speed obtained between the transvaginal and transabdominal ultrasound approaches was statistically significant at the anterior and posterior portions of the internal os ($p<0.05$), and not significant at the external os both anteriorly and posteriorly ($p>0.05$). The mean shear wave speed obtained in the phantom was 3.67m/s (±0.06m/s), and 3.72m/s (±0.04m/s) for the transabdominal and transvaginal ultrasound transducers respectively.

Conclusion The anterior portion of the cervix is more likely to produce reliable shear wave speeds than the posterior. Shear wave speeds obtained in the transvaginal approach are significantly greater at the internal os compared to the transabdominal approach, and are similar at the external os.

Keywords Shear wave, elastography, cervix, preterm birth, transvaginal ultrasound, transabdominal ultrasound

5.2 **Introduction**

Maternal cervical insufficiency and the implications for spontaneous preterm birth and its complications have been well documented.[1] The test with the greatest sensitivity for the determination of cervical insufficiency to date is assessment of cervical length using transvaginal (TV) ultrasound.[2] The sensitivity of this test for patients presenting with an elevated risk of preterm birth because of prior medical history, warrants the use of transvaginal cervical length to screen for cervical insufficiency in this population.[3] In the unselected population there is reduced sensitivity of this screening method, and there is work to do to firmly establish the best way of identifying women at risk of cervical insufficiency in this group.[3, 4] Universal cervical length screening with the TV ultrasound approach has not been recommended,[4] and there can also be a lack of acceptance of the TV ultrasound approach in some patients.[5]

However, the cervix is known to soften throughout pregnancy allowing it to dilate and efface prior to delivery of the fetus.[6] A premature reduction in cervical stiffness may be indicative of early softening of the cervix or imminent cervical insufficiency and impending preterm delivery of the fetus.[7] Shear wave elastography uses a modified ultrasound pulse called an acoustic radiation force impulse (ARFI) to determine how stiff the tissue is in the region being examined.[8] There have been previous works investigating the use of shear wave elastography to assess cervical strength, and a reduction in cervical stiffness identified by slower shear wave speed (SWS) has been observed in patients with clinical signs of preterm labour.[9] Shear wave elastography has also shown a gradual reduction in stiffness of the cervix throughout pregnancy, and a reduction in SWS in women who have been induced for labour with prostaglandins using a transvaginal ultrasound approach.[10-13]

Some ultrasound vendors provide shear wave technology on a curvilinear transabdominal (TA) transducer as well as the intracavity TV transducers. It has been shown that it is possible to assess the maternal cervix with shear wave elastography in both the TV and TA ultrasound approaches.[9,14] However it is expected that the different excitation frequencies of the ARFI pulses used for each transducer may produce different shear wave speeds in viscoelastic tissues.[15] It is not clear if shear wave speeds obtained in the maternal cervix would be concordant between the transabdominal and transvaginal ultrasound approaches and this could be of importance for clinical use. The aim of this work is to compare the use of TA and TV ultrasound approaches to obtain shear wave speeds (SWS) in the maternal cervix, and to compare the number of SWS measurements and the difference in SWS obtained in each approach.

5.3 Methods

5.3.1 Participant recruitment

A prospective cross sectional study of patients attending for their routine mid-trimester fetal morphology examination was performed between January 2017 and January 2019 at sites of SKG Radiology in Perth, Western Australia. Participants had varying pregnancy history and body habitus, and were from differing ethnicities. All participants were over 18 years of age, with a mean age of 28 years (18-41years), a mean of 2 prior pregnancies (1-9 pregnancies) and 1 prior birth (0-8 births). The mean gestation at the time of the examination was 19 weeks and 6 days (18 - 23 weeks). Ethics approval was obtained from the Curtin University Human Research Ethics Committee (HRE2016-0128) and the institutional review board. All participants were required to give informed consent to participate in the research and practice consent was also required for participants to undergo the transvaginal approach. Participants not able to give consent due to language barriers were excluded. Participants receiving progesterone treatment or current cerclage placement were also excluded. Participants could withdraw consent at any time. Data collection was performed by one sonographer (SO) with more than 10 years' experience in the field of obstetric ultrasound.

5.3.2 Imaging methodology

All imaging was performed on version 6 of the Canon Aplio 500 ultrasound machine (Otawara-shi, Tochigi, Japan). In both ultrasound approaches a continuous mode of acquisition was used with a frame rate of 0.4 frames per second, the elastogram map was stable for at least 3 seconds before SWS measurements were obtained.[16]

5.3.3 Transabdominal imaging

TA imaging utilised the 6C1 PVT-375BT curvilinear ultrasound transducer. Main pulse frequency was set to 2.2MHz. Elastogram map size was set at 20mm x 20mm. Elastogram opacity was set to 0.6. The region of interest (ROI) was set to a 5mm sphere to obtain SWS measurements.[14]

The maternal bladder was partially filled so as to provide a B-mode window for visualisation of the cervix and through transmission of the shear wave ARFI pulses to the cervix. With the patient in a supine position, the transducer was placed longitudinally just cephalad to the symphysis pubis in the midline. Transducer orientation was aligned to the length of the cervical canal and tilted to as close to a perpendicular approach to the canal as technically possible. Transducer pressure was reduced to a minimum whilst still maintaining an optimal B-mode image prior to the application of the shear wave.[14]

5.3.4 Transvaginal imaging

TV imaging utilised an 11C3 PVT-781VTE intra-cavity transducer. Main pulse frequency was set to 4MHz. Elastogram size was set at 20mm x 20mm. Elastogram opacity was set to 0.6. The ROI was set to a 5mm sphere was to obtain shear wave speed measurements.[17]

Transvaginal imaging was performed post void with transducer placement at the anterior fornix. Transducer orientation was aligned to the length of the cervical canal and the internal and external os were identified. Transducer pressure was reduced to a minimum whilst still maintaining an optimal B-mode image prior to the application of the shear wave.[14]

5.3.5 Shear wave measurements

Shear wave imaging was performed as an adjunct to the mid-trimester morphology examination. Measurements were obtained in the sagittal plane of the cervix. For both approaches SWS measurements were registered at the anterior and posterior portions of the internal and external cervical os (Figures 5.1 and 5.2). The ROI was placed in the portion of the cervix midway between the central canal and outer serosal layer, in the circumferential collagen and smooth muscle layer thought to be responsible for dilatation of the cervix in labour.[14, 17, 18] Three measurements of SWS were attempted at each portion of the cervix. Non-registered measurements were removed and the remaining measurements collated for analysis. All measurements with a non-uniform elastogram and erratic propagation map with a standard deviation (SD) greater than 20% of the mean speed within the 5mm ROI were considered to have a large variation of values within the 5mm ROI and an unreliable mean SWS, and were also removed during statistical analysis.[19] At least two SWS measurements that were considered reliable were required to calculate a mean speed for the region being interrogated.

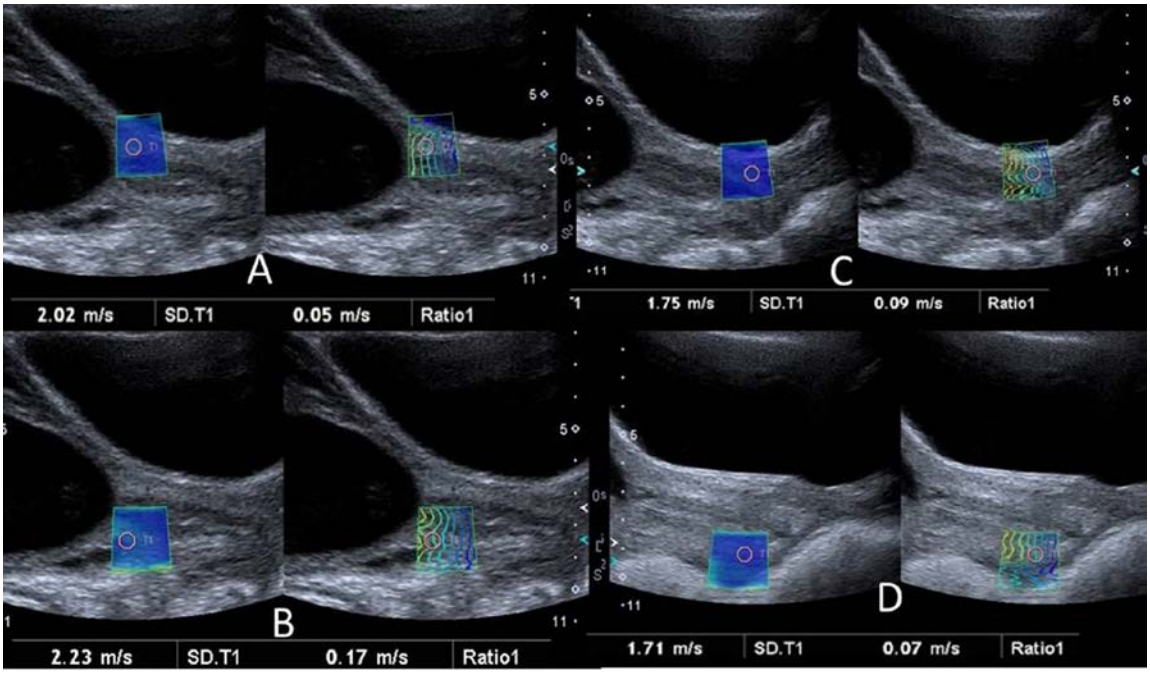


Figure 5.1: Example of elastogram and ROI placement for the transabdominal ultrasound approach. SWS (and SD) obtained as follows: A - Anterior Internal os 2.02m/s (SD 0.05m/s), B - Posterior Internal os 2.23m/s (SD 0.17m/s), C - Anterior External os 1.75m/s (SD 0.09m/s), D - Posterior External os 1.71m/s (SD 0.07m/s).

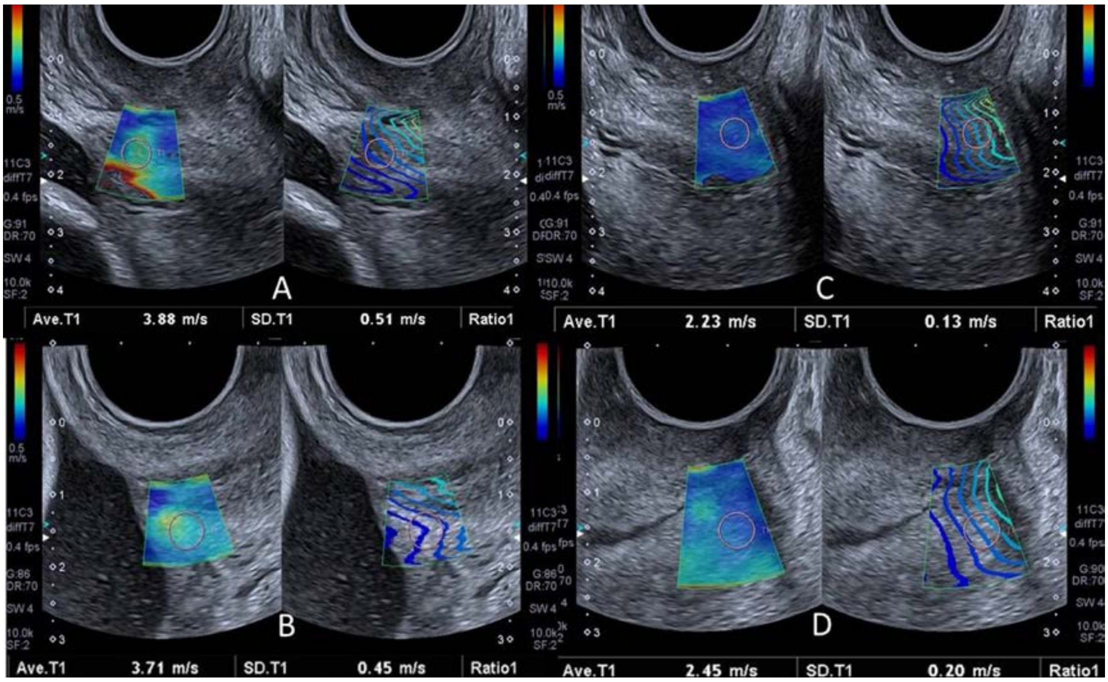


Figure 5.2: Example of elastogram and ROI placement for the transvaginal ultrasound approach. SWS (and SD) obtained as follows: A - Anterior Internal os 3.88m/s (SD 0.51m/s), B - Posterior Internal os 3.71m/s (SD 0.45m/s), C - Anterior External os 2.23m/s (SD 0.013m/s), D - Posterior External os 2.45m/s (SD 0.20m/s).

5.3.6 Phantom testing

Concordance of SWS was assessed between the 6C1 PVT-375BT transabdominal ultrasound transducer and 11C3 PVT-781VTE endocavity transducer using a quality assurance phantom. All imaging was performed on the Canon Aplio 500 ultrasound machine (Otawara-shi, Tochigi, Japan). Testing utilised the Elastography Quality Assurance (QA) Phantom model 049 (CIRS, Norfolk, VA, USA). Phantom background Young's Modulus is set at 25kPa, testing was performed on lesion IV with a Young's Modulus of 75kPa. As shown in Figures 5.3 and 5.4 the target lesion was set at a focal depth of 3cm for the TA probe and 15mm for the TV probe. Fifteen measurements were obtained with each transducer, in each lesion, and the mean value of these measurements was compared between both transducers.

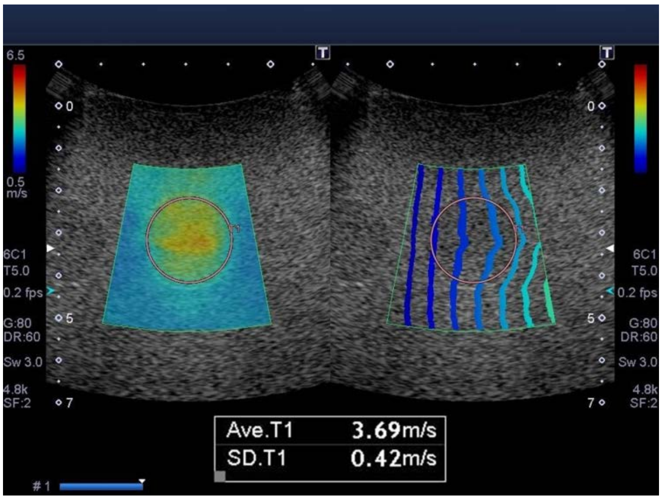


Figure 5.3: Shear wave speed obtained in QA phantom using the 6C1 PVT-375BT ultrasound transducer, mean speed of 3.69m/s (SD 0.42m/s)

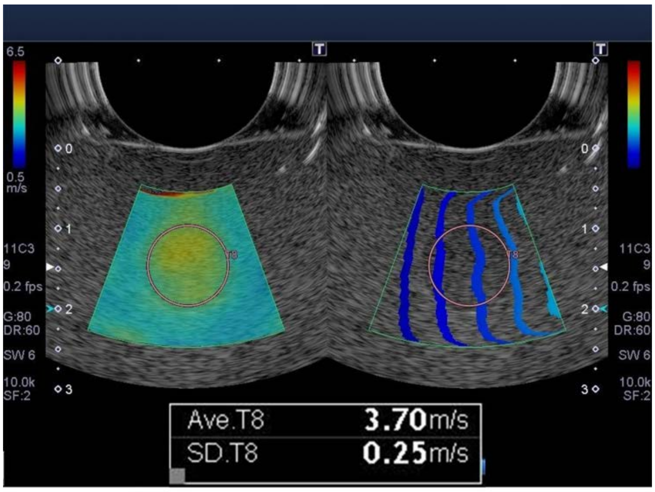


Figure 5.4: Shear wave speed obtained in QA phantom using 11C3 PVT-781VTE endocavity transducer, mean speed of 3.70m/s (SD 0.25m/s)

5.3.7 Statistical analysis

Descriptive data has been presented using the mean and SD. Mean shear wave speeds and SD obtained in each ultrasound approach and with each transducer have been assessed for differences between pairs using a one sample t-test, with the null hypothesis being that the difference in SWS obtained with the transabdominal and transvaginal transducers = 0. The results of the t-test are also presented in the form of Bland-Altman plots. The TV SWS was used as the reference method and the bias presented as the difference between this and the value of TA SWS. All variables input to the t-test were first tested for normality using a one sample Kolmogorov-Smirnov test. All data was found to be normal ($p>0.05$). Data was analysed using SPSS for Windows version 26 (SPSS V26.0, Chicago, USA).

5.4 **Results**

Thirty eight women agreed to participate with one participant withdrawing consent for the TV approach due to the extra time required to perform the shear wave measurements. The number of reliable SWS measurements obtained for each region of the cervix in both TA and TV approaches is shown at Table 5.1. The mean SWS obtained for each region is shown at Table 5.2.

Table 5.1: Number of shear wave speed measurements obtained in each region of the cervix on 37 participants

Region	External os Anterior	External os Posterior	Internal os Anterior	Internal os Posterior
Transabdominal approach	35	26	33	22
Transvaginal approach	37	30	32	17

Table 5.2: Mean shear wave speed and standard deviation (SD) obtained in each region of the cervix

Region	External os Anterior Mean speed	External os Posterior Mean speed	Internal os Anterior Mean speed	Internal os Posterior Mean speed
Transabdominal Approach	2.06m/s (0.36)	2.44m/s (0.48)	2.39m/s (0.37)	2.51m/s (0.42)
Transvaginal Approach	2.22m/s (0.43)	2.39m/s (0.46)	3.13m/s (0.78)	3.17m/s (0.55)

The mean difference in SWS between TV and TA SWS at the anterior portion of the external os was 0.15m/s (SE 0.09);t(34) = 1.80, *p*= 0.08. The Bland-Altman plot (Figure 5.3) demonstrates a positive bias of 0.15m/s and two values greater than the upper tolerance limit, with most of the values clustered around the line of no measurement bias. The mean difference in SWS between TV and TA SWS at the posterior portion of the external os was 0.07m/s (SE 0.13);t(21) = -0.50, *p*= 0.62. The Bland-Altman plot (Figure 5.4) demonstrates a negative bias of -0.07m/s and all values within the tolerance limits. The mean difference in SWS between TV and TA SWS at the anterior portion of the internal os was 0.67m/s (SE 0.15);t(26) = 4.43, *p*=0.00. The Bland-Altman plot (Figure 5.5) demonstrates a positive bias of 0.67m/s and a larger number of measurements greater than the line of no measurement bias. The mean difference in SWS between TV and TA SWS at the posterior portion of the internal os was 0.52m/s (SE 0.14);t(10) = 3.72, *p*=0.04. The Bland-Altman plot (Figure 5.6) demonstrates a significant positive bias of 0.52m/s with most values greater than the line of no measurement bias.

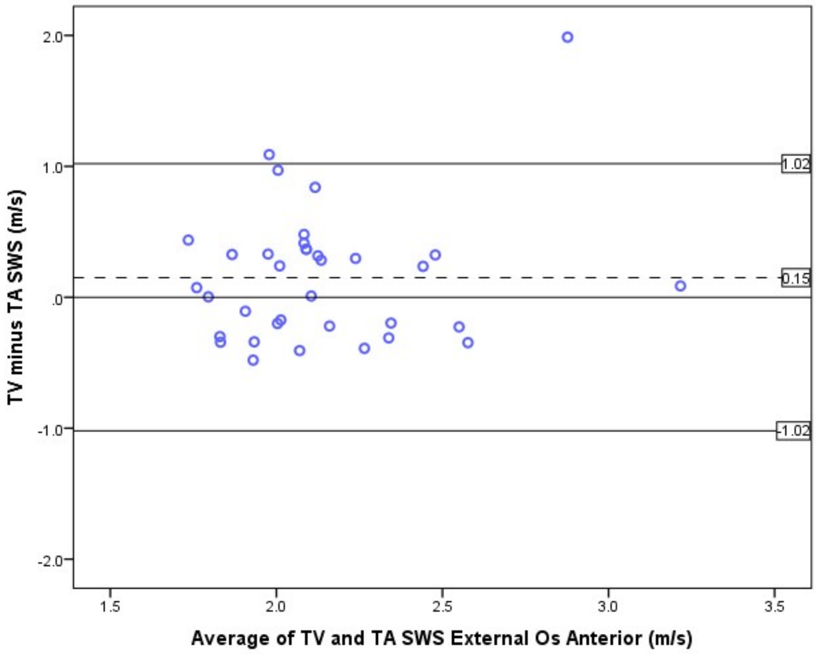


Figure 5.5: Bland-Altman plot demonstrating difference in SWS obtained between the TV and TA approaches at the anterior portion of the external os

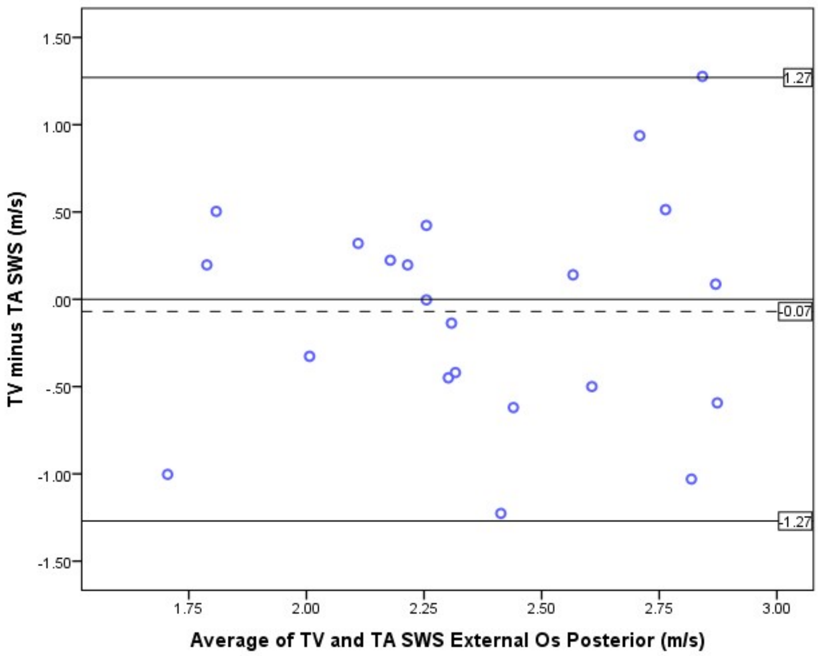


Figure 5.6: Bland-Altman plot demonstrating difference in SWS obtained between the TV and TA approaches at the posterior portion of the external os

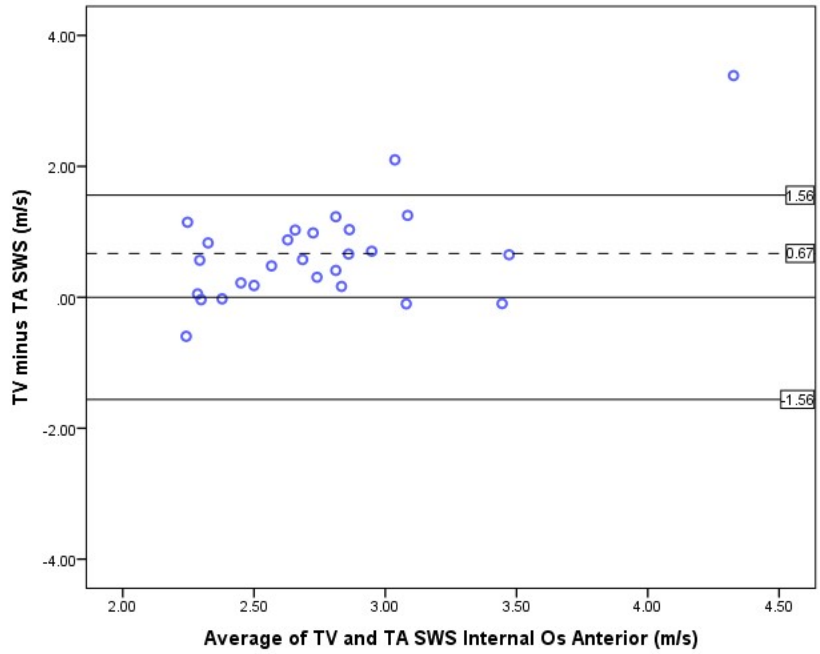


Figure 5.7: Bland-Altman plot demonstrating difference in SWS obtained between the TV and TA approaches at the anterior portion of the internal os

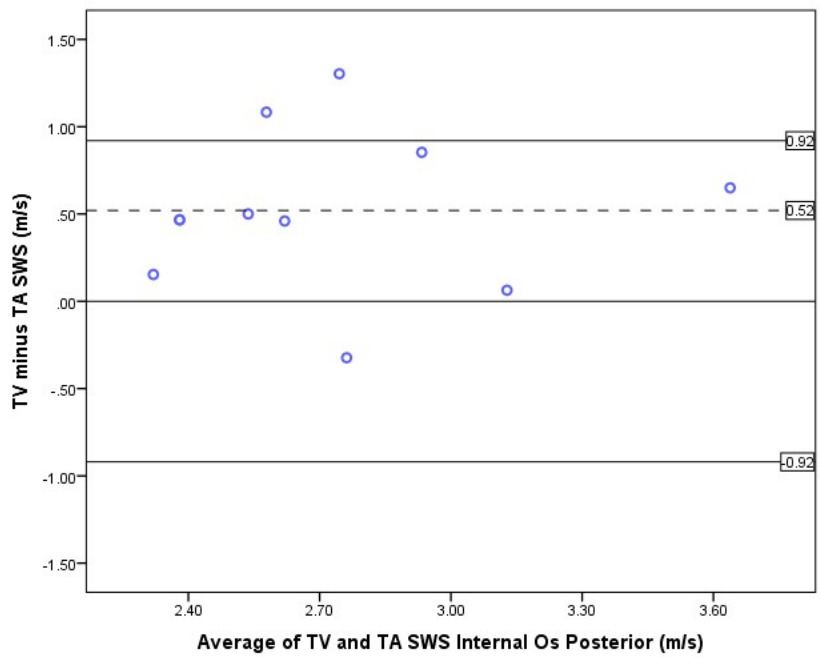


Figure 5.8: **Bland-Altman plot demonstrating difference in SWS obtained between the TV and TA approaches at the posterior portion of the internal os.**

5.4.1 Phantom testing

As demonstrated in Figure 5.9 the mean SWS obtained over 15 interrogations was 3.67m/s (±0.06m/s), and 3.72m/s (±0.04m/s), for the 6C1 curvilinear and the 11C3VTE intracavity transducers respectively.

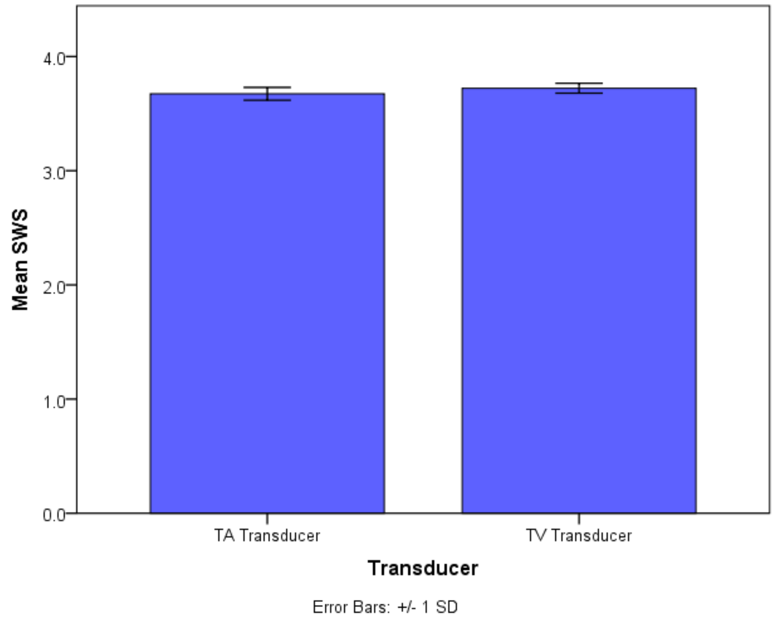


Figure 5.9: Bar graph demonstrating shear wave speeds (m/s) obtained for the ultrasound phantom testing using both the transabdominal and transvaginal ultrasound transducers over fifteen interrogations

5.5 Discussion

These results show that in most patients' measurements of shear wave speed can be obtained in both the transvaginal and transabdominal ultrasound approaches. This work has found that the anterior portion of the cervix was more likely to produce reliable shear wave speeds than the poster in both ultrasound approaches, with a greater number of measurements obtained in the anterior portions. These results have also shown that the shear wave speeds obtained with phantom testing are similar between the transabdominal and transvaginal transducer, but there were differences in shear wave speeds obtained in the transabdominal compared to the transvaginal ultrasound approach when applied to the maternal cervix, with the largest differences at the internal os. In both approaches faster shear wave speeds were registered at the internal os compared to the external os. Both approaches appear to have technical considerations that may impact on the success of transmission of the ARFI pulses and production of reliable shear waves in the cervix that will be discussed as follows.

As demonstrated in Table 5.1, the greatest number of SWS measurements obtained in both ultrasound approaches was at the anterior portion of the external os, followed by the anterior portion of the internal os. Whilst a greater number of SWS measurements were obtained at the posterior portion of the external os in the transvaginal approach than in the transabdominal approach. The posterior portion of the internal os registered the least number of reliable measurements in both ultrasound approaches, with SWS obtainable in less than half of the participants using the transvaginal approach, and a little over half of the participants in the transabdominal approach.

Depth of transmission of the main ARFI pulse to the ROI may be a factor in effective shear wave production, with less SWS measurements obtained in the posterior portions of the cervix in both approaches as discussed. The effective depth of transmission of the ARFI pulse used to produce shear waves is related to the frequency of the ARFI. Using the 11C3 VTE intracavity transducer it is expected that shear waves can be produced up to a depth of

3cm in an ultrasound phantom with an acoustic attenuation of 0.5 dB cm^{-1} MHz^{-1}.[17] Greater depths of transmission are achievable with the lower frequency ARFI pulse used with the 6C1 PVT transducer.[15] The acoustic attenuation of the cervix is 1.3 to 2.0 dB $cm^{-1}MHz^{-1}$, and thus it is expected that the depth of achievable shear wave production will be less in the cervix than in the preceding phantom example.[20] In the transvaginal approach the greatest distance from the transducer positioning at the anterior fornix is to the posterior portion of the internal os, and shear wave measurements were obtained in this region in only 17 of the 37 participants. The posterior portion of the cervix can also be more problematic in the TA approach, and as Table 5.1 demonstrates, less SWS measurements were obtained posteriorly than anteriorly in this approach also. Patients with a large body mass index and increasing distance from the transducer face to the cervix may also be problematic.[14] Figures 5.7 and 5.8 demonstrate loss of shear wave propagation in the posterior cervix in both TA and TV approaches.

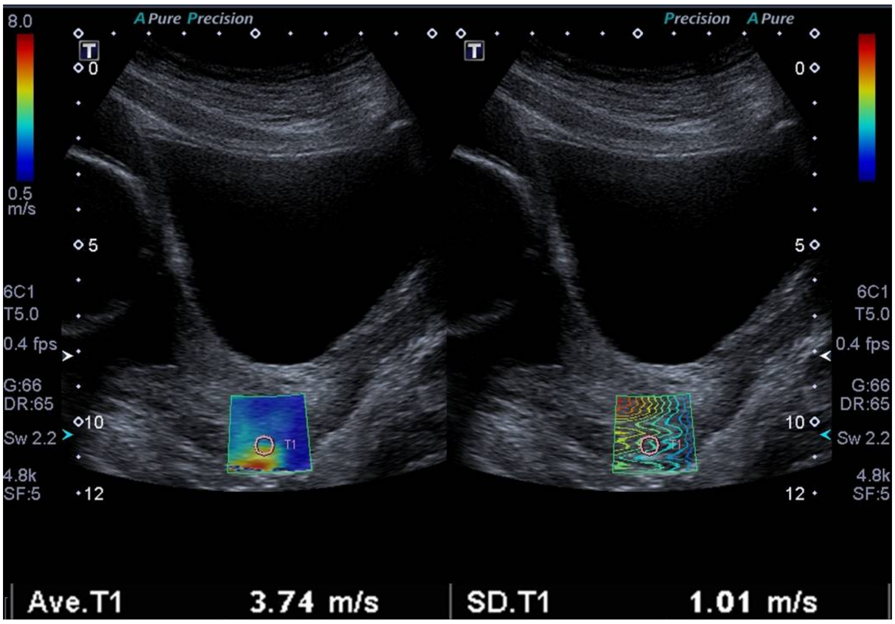


Figure 5.10: Example of loss of shear wave propagation in the posterior portion of the external os using the transabdominal ultrasound approach, demonstrating a non-uniform elastogram and erratic propagation lines at a depth greater than 10cm and high SD of 1.01m/s.

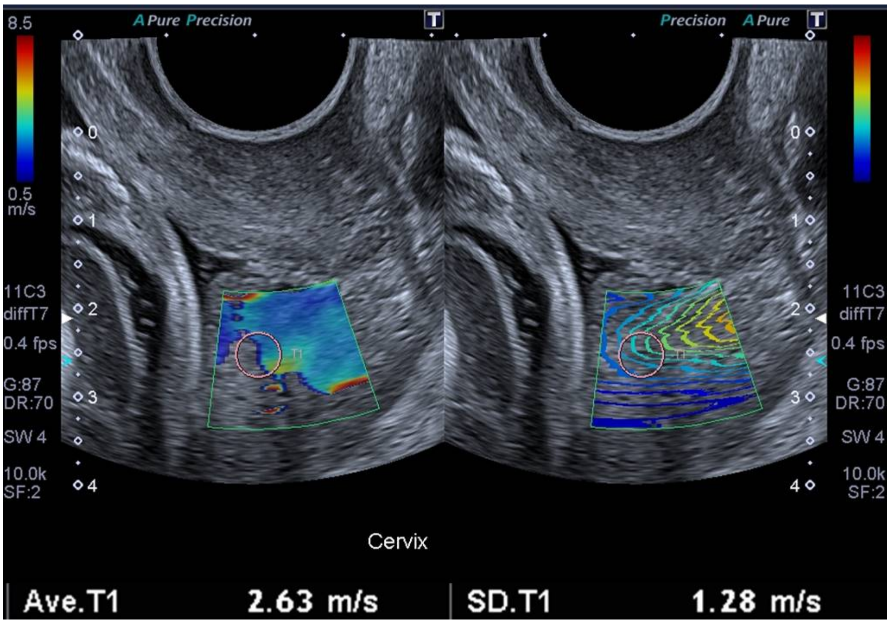


Figure 5.11: Example of loss of shear wave propagation shown in the posterior portion of the internal os using the transvaginal ultrasound approach, demonstrating loss of elastogram filling and erratic propagation lines and a high SD of 1.28m/s.

As the Bland-Altman plots demonstrate in Figures 5.3 to 5.6, and also demonstrated in Table 5.2, overall the TV approach has registered faster shear wave speeds than the TA approach, with the greatest differences in speed obtained at the anterior and posterior portions of the internal os. The mean SWS obtained at the anterior portion of the external os was minimally different between TV and TA approaches, with a very small difference obtained at the posterior portion of the external os.

Tissue boundaries encountered by the main ARFI pulses may also be contributing to a reduction of penetration of the ARFI pulses, and preventing shear wave penetration.[21] The cervical canal may be acting as a shear wave boundary and also contributing to the loss of shear wave production posteriorly. Anisotropy of tissues and shear wave artifacts may also produce inaccurate shear wave speeds.[21] Resultant shear wave speeds are also dependant on the frequency of the ARFI pulse in viscoelastic tissues, with higher frequencies as are used with a TV transducer expected to produce faster shear wave speeds.[21] As shown in Table 5.2, interestingly differences in the SWS obtained between the TV and TA approach was minimal at both the posterior and anterior portions of the external os. The TV approach produced slightly higher mean SWS at the anterior portion of the external os than the TA approach, and a marginally slower mean SWS than the TA approach at the posterior portion of the external os. The SWS obtained at the internal os was significantly greater in the TV approach compared to the TA approach in both anterior and posterior portions.

Pre-stress forces on the cervix have a significant effect on the resultant shear wave speed.[17] Transducer pressure should be kept to a minimum when obtaining SWS in the cervix. This can be problematic in the TV approach as transducer placement at the anterior fornix requires enough transducer pressure to obtain a B-mode image prior to obtaining SWS, and the anterior external os registered a slightly higher mean SWS in the TV approach compared to the TA approach. The distance from the transducer of the cervix and the presence of a partially full maternal bladder in the path of the ARFI pulse appears to reduce the effect of transducer pressure in the TA approach, with slower SWS obtained in the TA approach compared to the transvaginal approach. Maternal bladder filling may also cause issues, whilst an overfull maternal bladder may cause compression of the cervical tissues, a moderately full maternal bladder to a level just superior to the internal os is ideal. Under filling of the maternal bladder can be problematic in the transabdominal approach as the moderately filled maternal bladder appears to aid in the transmission of the ARFI pulses to the cervix.

As reported by other researchers [22], this study has also shown that the internal os produces faster shear wave speeds than the external os in both TA and TV approaches. This supports the theory that the internal os is stiffer and has a sphincter like effect in the retainment of a pregnancy.[18] This study also shows greater SWS was obtained in the posterior portion compared to the anterior portion of the cervix in both TA and TV approaches. Higher shear wave speeds have also been reported in the posterior cervix by other researchers using shear wave elastography,[11, 12] whereas researchers using strain elastography have found non substantial differences in stiffness between the posterior and anterior portions of the cervix,[23] or also reduced stiffness posteriorly.[24]

This study is limited by the use of one experienced sonographer to perform imaging and the use of one shear wave technology provider.

5.6 **Conclusion**

In summary the anterior portion of the cervix appears more likely to produce reliable shear wave speeds than the posterior portion in both transvaginal and transabdominal ultrasound approaches. The mean shear wave speeds obtained in the TV approach are significantly greater at the internal os, and similar to the TA approach at the external os. Further research into the use of shear wave elastography on the maternal cervix is needed to ascertain its usefulness in the prediction of spontaneous preterm birth. This study shows that there is potential for shear wave measurements to be obtained in either the transabdominal or transvaginal ultrasound approaches on the maternal cervix, but the differences in shear wave speeds obtained in each approach will need to be considered.

5.7 **References**

1. Myers KM, Feltovich H, Mazza E, et al. The mechanical role of the cervix in pregnancy. J Biomech. 2015; 48(9):1511-23.

2. Retzke JD, Sonek JD, Lehmann J, Yazdi B, Kagan KO. Comparison of three methods of cervical measurement in the first trimester: Single-line, two-line, and tracing. Prenatal Diagnosis. 2013; 33(3):262-268.

3. Olson Chen C. Ultrasound for cervical length. Ultrasound clinics. 2013; 8(1):1-11.

4. Larma JD, Iams JD. Is sonographic assessment of the cervix necessary and helpful? Clinical Obstetrics and Gynecology. 2012; 55(1):324-335.

5. Orzechowski KM, Boelig RC, Baxter JK, Berghella V. A universal transvaginal cervical length screening program for preterm birth prevention. Obstet Gynecol. 2014; 124(3):520-5.

6. Preis K, Swiatkowska-Freund M, Pankrac Z. Elastography in the examination of the uterine cervix before labour induction. Ginekol Pol. 2010; 81(10):757-761.

7. Callejas A, Gomez A, Melchor J, et al. Performance Study of a Torsional Wave Sensor and Cervical Tissue Characterization. Sensors (Basel). 2017; 17(9):2078

8. Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. Journal of the Acoustical Society of America. 2001; 110(1):625-634.

9. Agarwal S, Agarwal A, Joon P, Saraswat S, Chandak S. Fetal adrenal gland biometry and cervical elastography as predictors of preterm birth: A comparative study. Ultrasound (Leeds, England). 2018; 26(1):54-62.

10. Muller M, Aït-Belkacem D, Hessabi M, et al. Assessment of the Cervix in Pregnant Women Using Shear Wave Elastography: A Feasibility Study. Ultrasound in Medicine & Biology. 2015; 41(11):2789-2797.

11. Hernandez-Andrade E, Hassan SS, Ahn H, et al. Evaluation of cervical stiffness during pregnancy using semiquantitative ultrasound elastography. Ultrasound Obstet Gynecol. 2013; 41(2):152-161.

12. Peralta L, Molina FS, Melchor J, et al. Transient Elastography to Assess the Cervical Ripening during Pregnancy: A Preliminary Study. Ultraschall in Med. 2017; 38(04):395-402.

13. Carlson LC, Romero ST, Palmeri ML, et al. Changes in shear wave speed pre- and post-induction of labour: a feasibility study. Ultrasound in Obstetrics & Gynecology. 2015; 46(1):93-98.

14. O'Hara S, Zelesco M, Sun Z. Shear wave elastography of the maternal cervix: A transabdominal technique. Australasian Journal of Ultrasound in Medicine. 2018; 22(2):96-103.

15. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. Ultrasound Med Biol. 2015; 41(5):1126-47.

16. Thiele M, Detlefsen S, Sevelsted Moller L, et al. Transient and 2-Dimensional Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver Fibrosis and Cirrhosis. Gastroenterology. 2016; 150(1):123-33.

17. O'Hara S, Zelesco M, Sun Z. Shear Wave Elastography on the Uterine Cervix: Technical Development for the Transvaginal Approach. J Ultrasound Med. 2019; 38(4):1049-1060.

18. Nott JP, Bonney EA, Pickering JD, Simpson NAB. The structure and function of the cervix during pregnancy. Translational Research in Anatomy. 2016; 2:1-7.

19. O'Hara S, Zelesco M, Rocke K, Stevenson G, Sun Z. Reliability Indicators for 2-Dimensional Shear Wave Elastography. Journal of Ultrasound in Medicine. 2019; 38(11):3065-3071.

20. Palmeri M, Feltovich H, Homyk A, Carlson L, Hall T. Evaluating the feasibility of acoustic radiation force impulse shear wave elasticity imaging of the uterine cervix with an intracavity array: a simulation study. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control. 2013; 60(10):2053-2064.

21. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med. 2013; 34(2):169-84.

22. Carlson LC, Feltovich H, Palmeri ML, Rio AMd, Hall TJ. Statistical analysis of shear wave speed in the uterine cervix. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control. 2014; 61(10):1651-1660.

23. Swiatkowska-Freund M, Preis K. Elastography of the uterine cervix: implications for success of induction of labour. Ultrasound Obstet Gynecol. 2011; 38(1):52-56.

24. Molina FS, Gómez LF, Florido J, Padilla MC, Nicolaides KH. Quantification of cervical elastography: a reproducibility study. Ultrasound Obstet Gynecol. 2012; 39(6):685-689.

Chapter 6

Can shear wave elastography

on the maternal cervix be of use for the prediction

of preterm birth?

6.1 **Abstract**

Objectives The main goals of this work were to assess the use of shear wave elastrography on the maternal cervix using a transabdominal ultrasound approach, and to predict the likelihood of preterm birth.

Methods Measurements of shear wave speed were obtained at the anterior and posterior portions of the internal and external cervical os on 504 participants. A total of 455 participants were contacted following the expected date of birth of the fetus and birth details were obtained.

Results The anterior and posterior portion of the internal os showed a significant correlation between shear wave speed and time until delivery of the fetus, R^2 Linear = 0.024 (p=0.012) and R^2 Linear = 0.017 (p=0.05) . A ratio of the anterior portion of internal os over the anterior portion of the external os showed a significant correlation with the time until delivery of the fetus, R^2 Linear = 0.016 (p=0.043).

Conclusion It appears that a transabdominal ultrasound technique can be used to identify a reduction in shear wave speeds at the internal os in the mid-trimester in women who have a subsequent preterm birth.

Keywords Elastography, shear wave, preterm, birth, ultrasound

6.2 **Introduction**

The ramifications of preterm birth and its impact on fetal mortality and morbidity are well known.[1] There are numerous environmental reasons that will increase the likelihood of preterm birth occurring, with one of the highest risks being a previous preterm birth.[2] During pregnancy, a premature softening of the cervix, known as cervical insufficiency, is strongly associated with subsequent spontaneous preterm birth.[3]

The current gold standard for the assessment of cervical insufficiency is the identification of a reduced cervical length as seen on transvaginal ultrasound,[4] the shorter the length is found to be, the greater the risk of preterm birth.[5-7] Even so many women with a cervical length that is reduced will give birth at term, and also many preterm births occur in women who register a cervical length within the normal range in the mid-trimester.[8] A cervical length that is short has a greater sensitivity for subsequent spontaneous preterm birth in women who present with a high risk of preterm birth due to medical history, with a decreased sensitivity in the unselected population.[9-11] Due to this decreased sensitivity, the appropriate method for screening of the cervical length in the low risk population is still debatable, with some authors suggesting that a transabdominal technique can be used initially followed by the transvaginal cervical length when necessary.[1]

The cervix is composed of an innermost layer of smooth muscle and collagen parallel to and wrapping around, the central canal, with a mid-layer composed of collagen and smooth muscle cells wrapping circumferentially around this inner layer.[12, 13] There is a higher concentration of smooth muscle cells and greater organisation of this circumferential layer at the internal os than at the external cervical os, creating a sphincter like structure at the internal os.[13] The cervix is tasked with maintaining strength throughout the pregnancy until it then softens and dilates prior to delivery of the fetus.[3] Softening of the cervix commences at the internal os and therefore limits the usefulness of manual palpation, which is not only subjective to the clinician but also limited to assessment of the external cervical os.[3, 14, 15]

Ultrasound shear wave elastography technology can be used to evaluate the stiffness of tissues in a region of the body that is remote from the transducer.[16] This technology has been applied to the maternal cervix using a transvaginal ultrasound approach.[17, 18 19] There has also been some work with a transabdominal ultrasound approach.[20] Work is needed to assess if it is possible to predict the likelihood of cervical insufficiency and subsequent preterm birth with shear wave elastography with greater sensitivity than cervical length.

Guidelines for assessment of cervical length do not support universal screening of the cervix with a transvaginal approach in the mid-trimester, and this work investigates the use of a transabdominal (TA) ultrasound approach to obtain shear wave measurements in the cervix for the prediction of cervical insufficiency and imminent spontaneous preterm birth.[1, 21] The main aim of this work was to assess if it is possible to define a shear wave speed below which the chance of subsequent spontaneous preterm birth is increased. A secondary aim was to formulate a ratio of speeds obtained at the internal cervical os divided by the speeds obtained at the external cervical os, and a cut off ratio below which preterm birth is likely. Differences in shear wave speed obtained in participants with differing ethnicity, age, gestational status and weeks of pregnancy at presentation has also been assessed.

6.3 **Methods**

6.3.1 Participant recruitment

A prospective cross sectional study of patients attending for routine mid-trimester fetal morphology examination was performed between September 2016 and June 2019 at sites of SKG Radiology in Perth, Western Australia. Participants were contacted by the primary sonographer (SO) following the expected birth of the fetus to obtain details of the date of birth and mode of delivery. Participants had varying pregnancy history and body habitus, and were from differing ethnicities. All participants were over the age of 18 years, with a mean age of 29 years (18-51years), a mean of 2 prior pregnancies (1-9 pregnancies) and 1 prior birth (0-8 births). The mean gestation at the time of the examination was 19 weeks and 6 days (16 - 27 weeks). Ethics approval was obtained from the Curtin University Human Research Ethics Committee (HRE2016-0128) and the institutional review board. All participants were required to give informed consent to participate in the research. Participants who were not able to give informed consent due to language barriers were excluded. Participants receiving progesterone treatment or current cerclage placement were also excluded. Participants could withdraw consent at any time. Imaging data collection was performed by sonographers with less than and more than 10 years of experience in the field of obstetric ultrasound.

6.3.2 Inter-operator testing

Inter-operator testing was double blinded and performed on 15 participants. The primary sonographer has over 10 years of experience in the field of obstetric ultrasound. Two secondary sonographers had both greater and less than 10 years of experience respectively in the field of obstetric ultrasound. All sonographers were experienced in the use of shear wave elastography in liver assessment and also have experience in gynaecological and obstetric applications of ultrasound. For each participant the primary sonographer obtained shear wave readings in all portions of the cervix. The secondary sonographer obtained the same set of readings. Sonographers were blind to the readings being obtained by the other sonographer. The mean speed that was obtained by each sonographer was then assessed to determine the level of agreement between sonographers.

6.3.3 Imaging methodology

All imaging was performed using version 6 of the Canon Aplio 500 ultrasound machine (Otawara-shi, Tochigi, Japan). Two dimensional (2D) shear wave elastography was used to obtain measurements of shear wave speed. A continuous mode of acquisition was used with a frame rate of 0.4 frames per second, the elastogram map was stable for at least 3 seconds before region of interest (ROI) placement to obtain the measurements of SWS.[22]

6.3.4 Ultrasound imaging

2D shear wave elastography imaging was performed during the mid-trimester fetal morphology ultrasound examination. Measurements of the length of the cervix were performed as per the guidelines for cervical length measurement for the prediction of preterm birth from the Royal Australian College of Obstetricians and Gynaecologists.[21]

Ultrasound 2D shear wave elastography imaging was performed with the 6C1 PVT-375BT curvilinear ultrasound transducer. Main pulse frequency was set to 2.2MHz. Elastogram map size was set at 20mm x 20mm. Elastogram opacity was set to 0.6. The ROI was set at a 5mm sphere to obtain SWS measurements.[23] The maternal bladder was partially filled so as to provide a B-mode window for visualisation of the cervix and through transmission of the shear wave ARFI pulses to the cervix. With the patient in a supine position, the transducer was placed longitudinally just cephalad to the symphysis pubis in the midline. Transducer orientation was aligned to the length of the cervical canal, and tilted to obtain as close to a perpendicular approach of the main shear wave pulses to the canal as technically possible. Transducer pressure was reduced to a minimum whilst still maintaining an optimal B-mode image prior to the application of the shear wave.[23]

6.3.5 Shear wave measurements

Measurements of the speed of shear wave movement were registered in the sagittal plane of the cervix at both the posterior and anterior portions of the external and internal cervical os (Figure 6.1). The ROI was placed in the portion of the cervix midway between the central canal and outer serosal layer in the circumferential collagen and smooth muscle layer region thought to be responsible for dilatation of the cervix in labour.[12, 13] Three measurements of SWS were attempted at each portion of the cervix. All measurements obtained were collated for analysis. All measurements with a non-uniform elastogram and erratic propagation map and a standard deviation (SD) greater than 20% of the mean speed within the 5mm ROI, were considered to have a large variation of values within the 5mm ROI and an unreliable mean SWS, and were removed during statistical analysis.[24] At least two measurements that were considered to be reliable were required to calculate a mean speed for the region being interrogated.

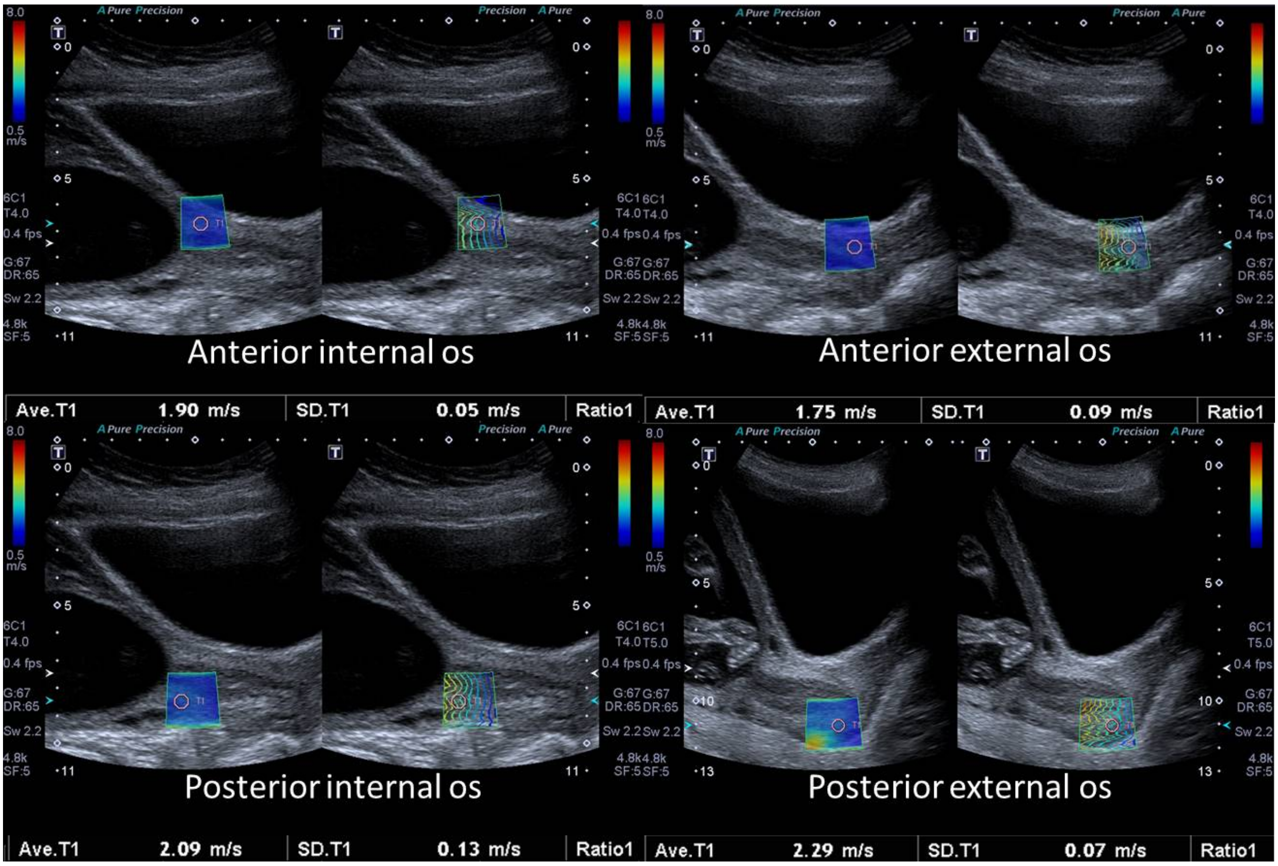


Figure 6.1: Example of the transabdominal ultrasound approach using 2D shear wave elastography, demonstrating placement of elastogram and ROI placement at each region of the cervix.

6.3.6 Statistical analysis

Descriptive data has been presented using the mean shear wave speed and standard deviation (SD). Participants who received subsequent vaginal progesterone treatment or cervical cerclage following participation due to a shortened cervical length or a medically indicated preterm birth were removed for analysis of shear wave speed and time to delivery. Linear regression analysis correlating the shear wave speed at each region of the cervix and ratio of the internal to external os, to the dependant variable of time between the ultrasound examination and days to delivery has been performed with a level of statistical significance set at $p = 0.05$. Results have been presented using scatterplots with the dependant variable on the y axis and demonstrating the R^2 value and p value obtained.

Agreement between sonographers was assessed using the Intra-class Correlation Coefficient (ICC). The ICC defines poor agreement as being a value close to 0 and a high level defined as 1. ICC estimates and their 95% confidence intervals were calculated based on a mean rating ($k = 3$), absolute agreement, 2-way mixed effects model.[25, 26]

SPSS for Windows version 26 (SPSS V26.0, Chicago, USA) was used to analyse the data.

6.4 **Results**

Over the 33 month duration of data collection, 504 women enrolled to participate in the study. Birth details have been obtained on 455 participants, with a total of 49 participants either lost to follow up or excluded due to receiving progesterone treatment or cerclage placement on the cervix. Of the 455 participants 171 were in their first pregnancy, 217 had a previous vaginal birth with 58 participants having a prior caesarean section (c-section) delivery, and 9 participants both vaginal and c-section. Twenty of the participants had a preterm birth in a previous pregnancy. For the 455 participants that birth details were obtained from, 75 had a planned c-section delivery, 277 went into spontaneous labour, 103 underwent labour induction and out of these 68 patients had a subsequent emergency c-section delivery.

The overall preterm birth rate for the 455 participants was 6.6%, with eight of these participants undergoing a medically indicated preterm delivery between 32 and 37 weeks of pregnancy. Twenty two patients or 4.8% of participants had a preterm birth following spontaneous labour.

The mean shear wave speed and standard deviation obtained at each region of the cervix dependant on maternal age, weeks of pregnancy at presentation, gestational status and ethnicity has been presented in Table 6.1. Table 6.2 presents the mean shear wave speed and standard deviation obtained in each region of the cervix for participant's dependant on the previous mode of delivery in prior pregnancies or previous preterm births.

Table 6.1: Summary of mean shear wave speed(m/s) and standard deviation (SD) at each region of the cervix for all 455 participants dependant on differing patient characteristics.

Participant characteristics	Number of participants	Anterior internal os	Posterior internal os	Anterior external os	Posterior external os
Age range 18-23years	65	2.43 (0.49)	2.48 (0.44)	2.02 (0.38)	2.35 (0.49)
Age range 24-29years	182	2.52 (0.54)	2.6 (0.54)	2.02 (0.0.34)	2.36 (0.47)
Age range 30-35years	164	2.52 (0.57)	2.58 (0.47)	2.09 (0.0.38)	2.37 (0.43)
Age range 36-41years	41	2.54 (0.45)	2.67 (0.61)	2.06 (0.38)	2.43 (0.41)
Age range 42-50years	3	2.25 (0.42)	2.7 (0.53)	2.92 (SD 1.2)	2.29
Weeks of pregnancy 16-18weeks	10	2.34 (0.73)	2.53 (0.68)	1.94 (0.16)	2.08 (0.40)
Weeks of pregnancy 18-20weeks	305	2.52 (0.55)	2.60 (0.51)	2.06 (0.38)	2.39 (0.45)
Weeks of pregnancy 20-22weeks	127	2.50 (0.51)	2.54 (0.50)	2.07 (0.39)	2.36 (0.46)
Weeks of pregnancy 22-24weeks	6	2.39 (0.45)	2.44 (0.54)	1.88 (0.31)	2.08 (0.32)
Weeks of pregnancy 24-28weeks	7	2.35 (0.24)	2.56 (0.32)	1.88 (0.28)	1.97 (0.30)
1st pregnancy	147	2.51 (0.54)	2.61 (0.53)	2.02 (0.36)	2.38 (0.45)
2nd to 5th pregnancy	294	2.49 (0.52)	2.56 (0.50)	2.07 (0.39)	2.35 (0.45)
>5 pregnancies	14	2.82 (0.63)	2.70 (0.47)	2.07 (0.46)	2.60 (0.57)
European	320	2.51 (0.53)	2.60 (0.53)	2.05 (0.37)	2.37 (0.47)
East Asian	74	2.47 (0.59)	2.53 (0.45)	2.05 (0.41)	2.36 (0.41)
African	14	2.34 (0.41)	2.64 (0.52)	2.01 (0.36)	2.33 (0.49)
Indigenous Australian	9	2.73 (0.81)	2.41 (0.26)	2.22 (0.51)	2.36 (0.35)
Indian	23	2.44 (0.42)	2.64 (0.50)	2.05 (0.37)	2.31 (0.31)
Maori	15	2.71 (0.54)	2.41 (0.42)	2.09 (0.35)	2.39 (0.55)

Table 6.2: Summary of mean shear wave speed (m/s) and standard deviation (SD) at each region of the cervix for all 455 participants, dependant on details of delivery of the fetus in a previous pregnancy and for women in their first pregnancy.

Participant characteristics	Number of participants	Anterior internal os	Posterior internal os	Anterior external os	Posterior external os
Previous vaginal delivery/s	217	2.52 (0.55)	2.58 (0.51)	2.04 (0.39)	2.33 (0.44)
Previous c-section/s	58	2.40 (0.44)	2.53 (0.43)	2.11 (0.38)	2.36 (0.41)
Previous vaginal and c-section/s	9	2.70 (0.72)	2.50 (0.58)	2.07 (0.38)	2.78 (0.50)
Previous term delivery/s	270	2.48 (0.50)	2.56 (0.49)	2.06 (0.39)	2.34 (0.44)
Previous preterm delivery/s	19	2.76 (0.86)	2.59 (0.42)	2.03 (0.41)	2.45 (0.47)
No previous delivery	166	2.51 (0.54)	2.61 (0.53)	2.05 (0.38)	2.37 (0.45)

The correlation of shear wave speed (m/s) to the time elapsed following the scan till the birth of the fetus, inclusive of the R^2 value and *p* value obtained for 447 women undergoing both spontaneous labour at any time throughout the pregnancy and labour induction or planned c-section at term, is presented in the form of scatterplots (Figures 6.2 to 6.5). The ratio formulated of the internal os divided by the external os at the anterior and posterior portions of the cervix has also been correlated to the time elapsed following the scan till birth of the fetus (Figures 6.6 and 6.7) The mean shear wave speed and SD for each region of the cervix and the ratio of internal os to external os for both anterior and posterior portions of the cervix dependant on when the fetus was delivered women can be seen at Table 6.3. The bar graphs presented at Figures 6.8 to 6.11 demonstrate the differences in shear wave speeds obtained at each region of the cervix for the 447 participants depending on the mode of delivery of the fetus and the weeks of gestation at delivery.

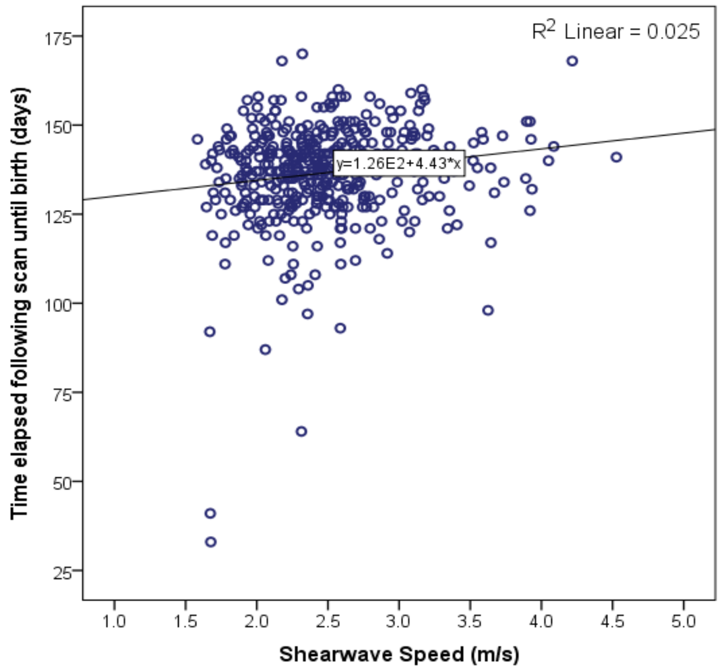


Figure 6.2: Correlation of shear wave speed to the time elapsed following the scan until birth of the fetus at the anterior portion of the internal os; R^2 Linear = 0.025 (*p*=0.001)

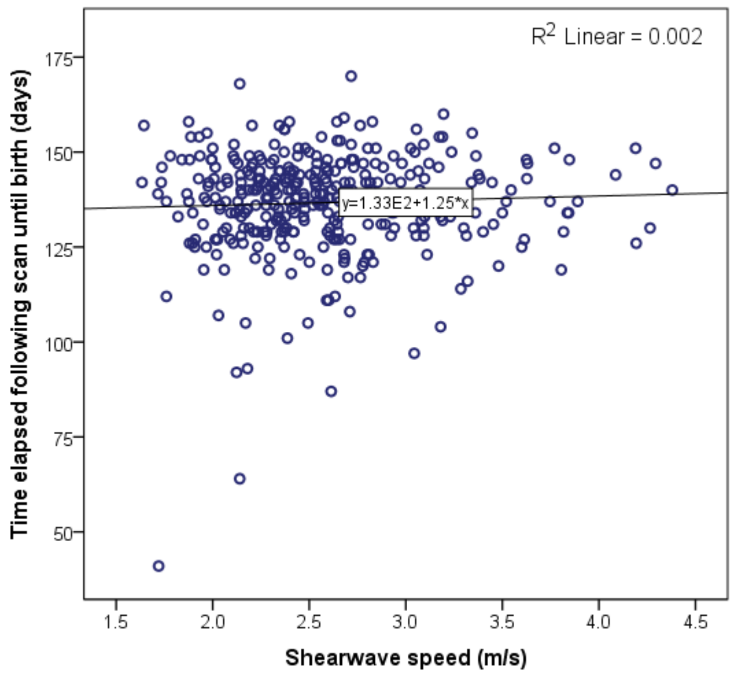


Figure 6.3: Correlation of shear wave speed to the time elapsed following the scan until birth of the fetus at the posterior portion of the internal os; R^2 Linear = 0.002 (*p*=0.368)

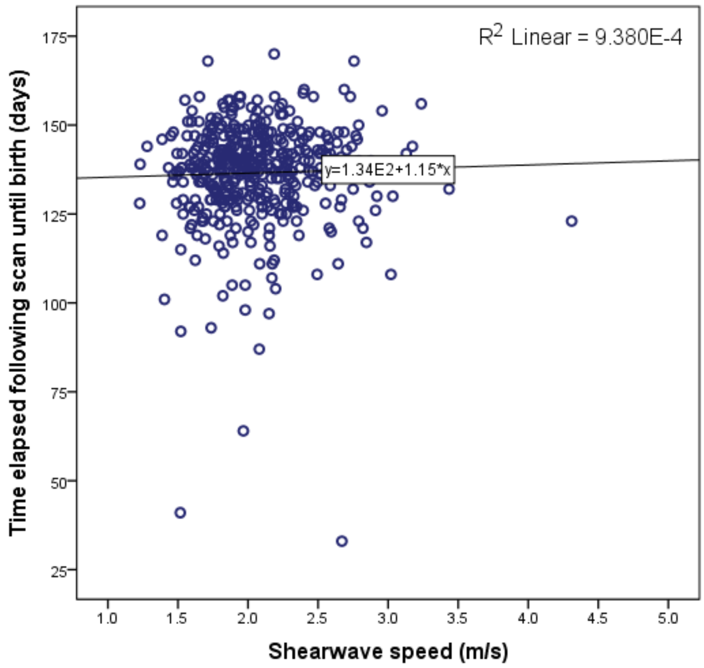


Figure 6.4: Correlation of shear wave speed to the time elapsed following the scan until birth of the fetus at the anterior portion of the external os; R^2 Linear <0.001 (*p*=0.526)

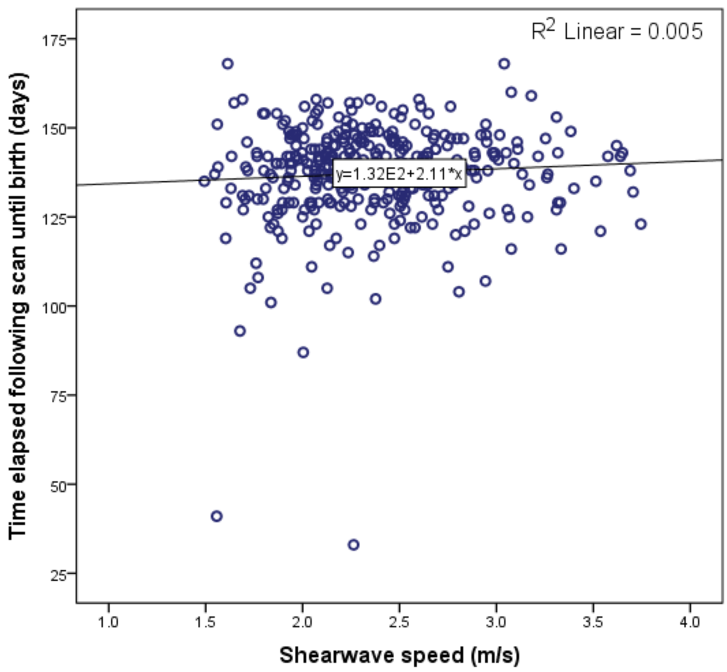


Figure 6.5: Correlation of shear wave speed to the time elapsed following the scan until birth of the fetus at the posterior portion of the external os; R^2 Linear = 0.005 (*p*=0.197)

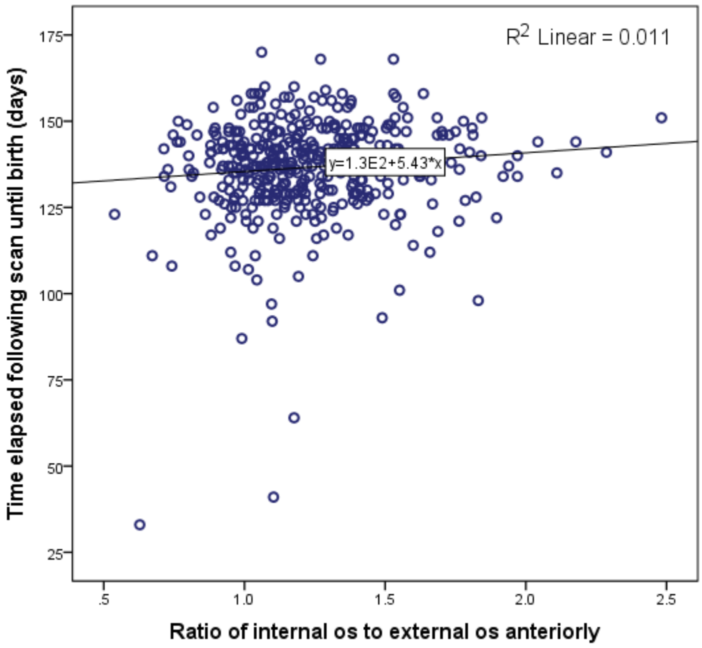


Figure 6.6: Correlation of the ratio of the internal os/external os in the anterior portion of the cervix, to the time elapsed following the scan until birth of the fetus; R^2 Linear = 0.011 (*p*=0.030)

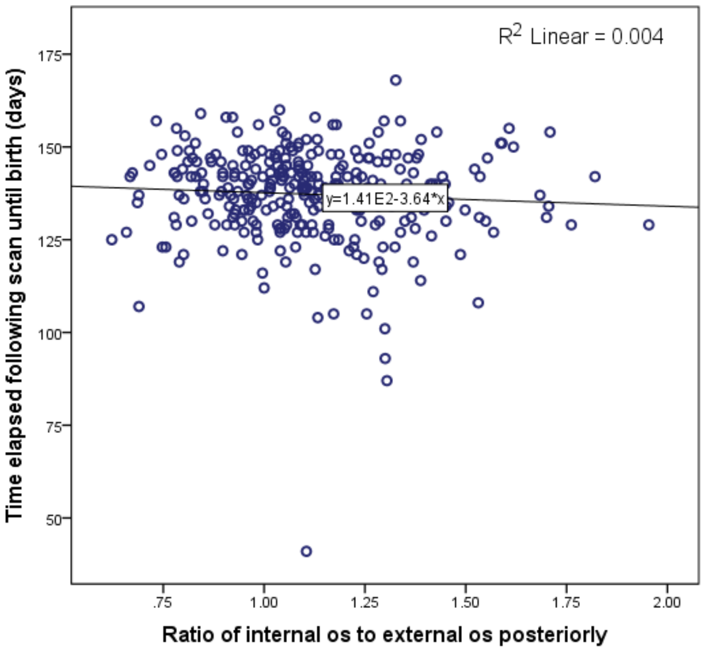


Figure 6.7: Correlation of the ratio of the internal os/external os in the posterior portion of the cervix to the time elapsed following the scan until birth of the fetus; R^2 Linear = 0.004 (*p*=0.255)

Table 6.3: Mean shear wave speed (m/s) and (SD) and also the ratio of internal os over external os at each region of the cervix for extremely preterm, very preterm, moderate to late preterm and term and post term deliveries excluding medically indicated preterm births.

Gestation at delivery of fetus	Number of cases	Anterior internal os	Posterior internal os	Anterior external os	Posterior external os	Anterior ratio internal os/external os	Posterior ratio internal os/external os
>28 weeks	2	1.67 (0.01)	1.72	2.09 (0.81)	1.91 (0.50)	0.87 (0.34)	1.10
28-32 weeks	1	2.31	2.14	1.97		1.18	
32-37 weeks	19	2.46 (0.59)	2.47 (0.39)	1.99 (0.43)	2.37 (0.48)	1.24 (0.29)	1.08 (0.24)
37-40 weeks	302	2.50 (0.54)	2.61 (0.52)	2.05 (0.38)	2.38 (0.47)	1.24 (0.29)	1.12 (0.24)
>40 weeks	123	2.58 (0.52)	2.53 (0.48)	2.09 (0.37)	2.36 (0.46)	1.26 (0.26)	1.09 (0.20)

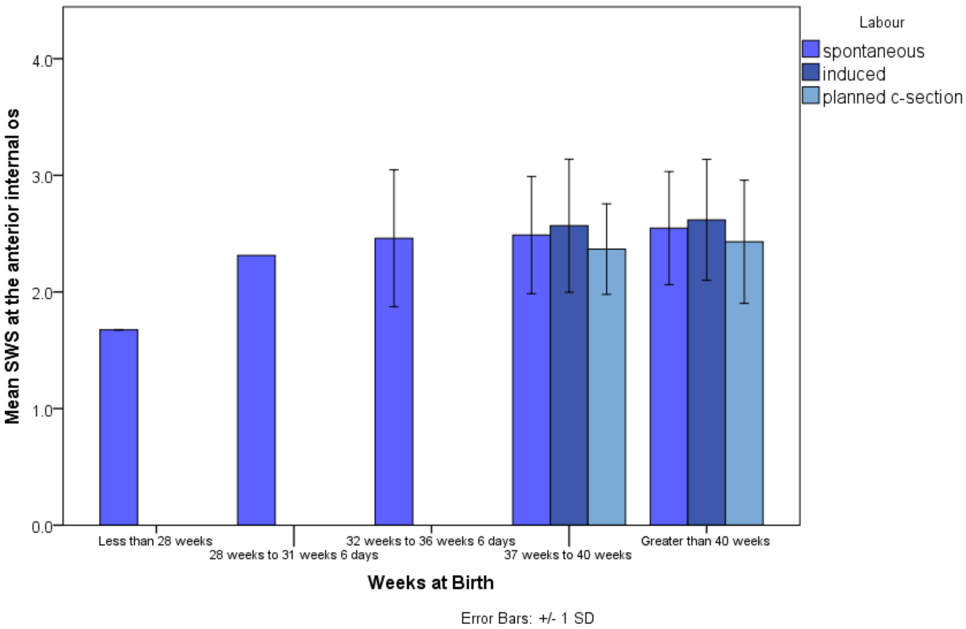


Figure 6.8: Graph of mean shear wave speed obtained in the anterior portion of the internal os for 447 participants with spontaneous labour, induced labour or planned caesarean section and the weeks of delivery.

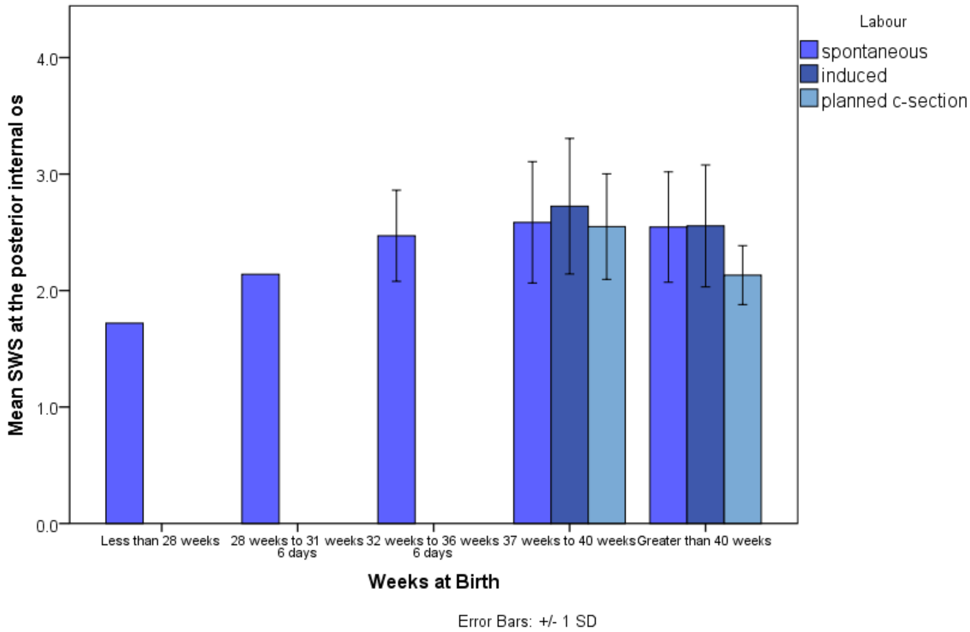


Figure 6.9: Graph of mean shear wave speed obtained in the posterior portion of the internal os for 447 participants with spontaneous labour, induced labour or planned caesarean section and the weeks of delivery.

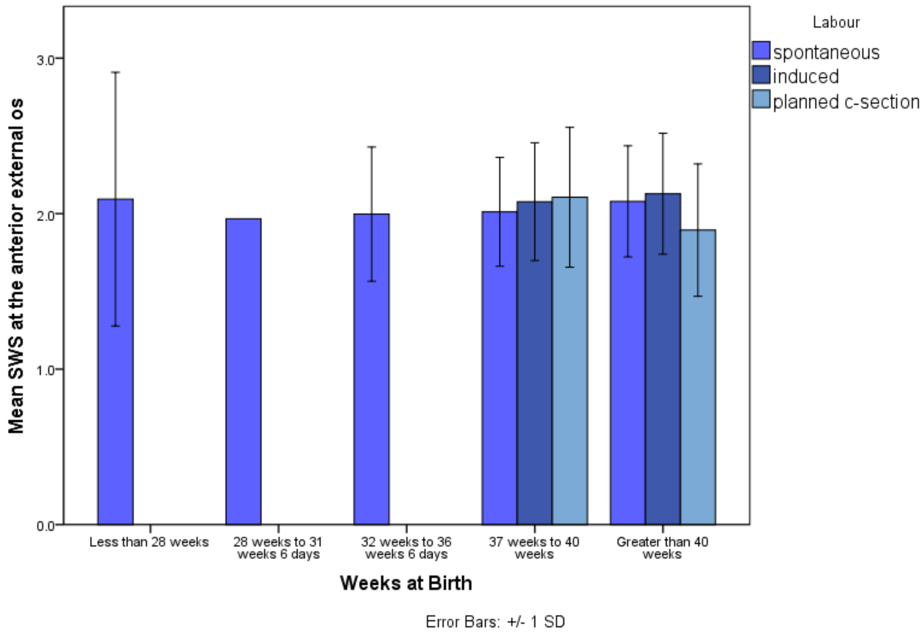


Figure 6.10: Graph of mean shear wave speed obtained in the anterior portion of the external os for 447 participants with spontaneous labour, induced labour or planned caesarean section and the weeks of delivery.

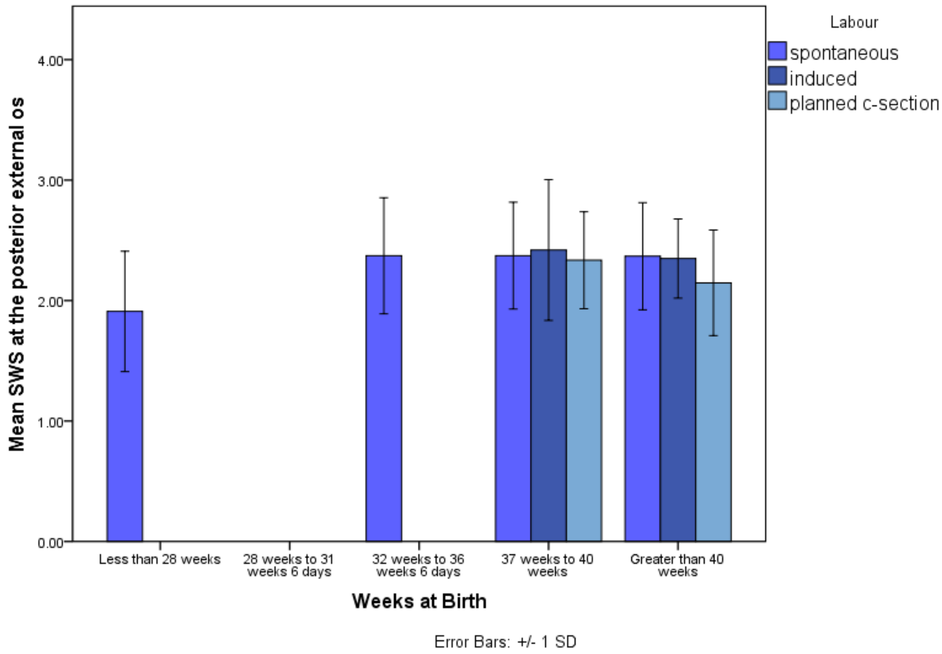


Figure 6.11: Graph of mean shear wave speed obtained in the posterior portion of the external os for 447 participants with spontaneous labour, induced labour or planned caesarean section and the weeks of delivery.

6.4.1 Spontaneous births

The correlation of shear wave speed (m/s) to the time elapsed following the scan till the birth of the fetus, inclusive of the R^2 value and *p* value obtained for 277 women undergoing spontaneous labour only are presented in the form of scatterplots (Figures 6.12 to 6.15). The ratio formulated of the internal os divided by the external os at the anterior and posterior portions of the cervix has also been correlated to the time elapsed following the scan till birth of the fetus for spontaneous births only (Figures 6.16 and 6.17).

These results were analysed further to assess the linear correlation for women who presented for the ultrasound examination between 18 weeks and 20 weeks and six days of pregnancy and had a subsequent spontaneous labour in the pregnancy. The correlation of shear wave speed and time to birth inclusive of the R^2 value and *p* value obtained for 246 women who presented at this time, and the ratio of the internal to external os and correlation with time to birth can be seen at Figures 6.18 to 6.23.

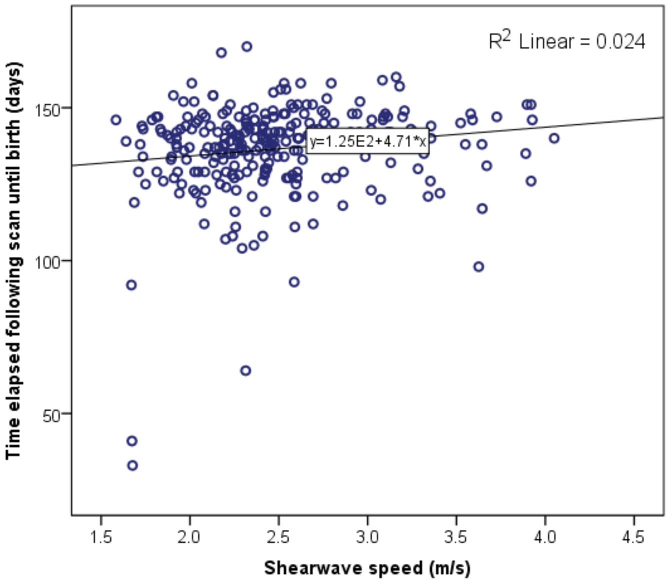


Figure 6.12: Correlation of shear wave speed to the time elapsed following the scan until the birth of the fetus at the anterior portion of the internal os; R^2 Linear = 0.024 (*p*=0.012) for 277 spontaneous births.

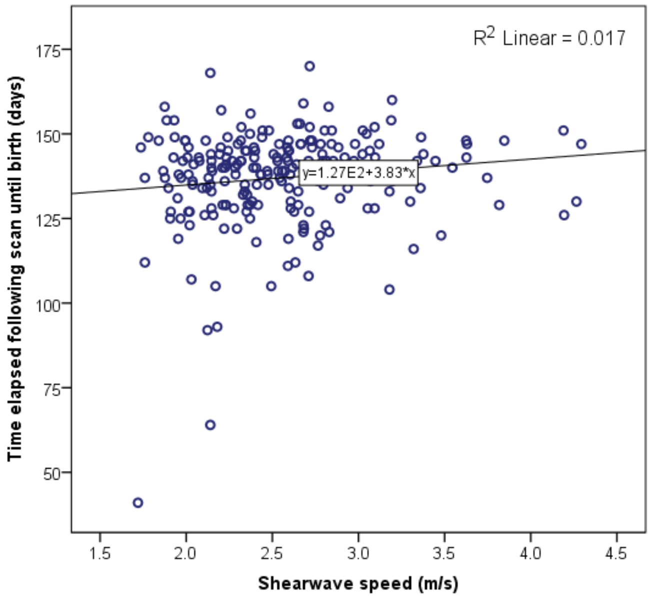


Figure 6.13: Correlation of shear wave speed to the time elapsed following the scan until the birth of the fetus at the posterior portion of the internal os; R^2 Linear = 0.017 (*p*=0.05) for 277 spontaneous births.

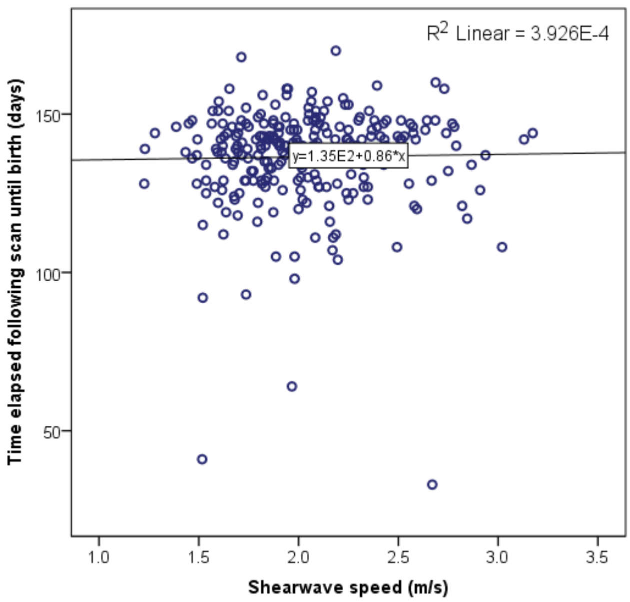


Figure 6.14: Correlation of shear wave speed to the time elapsed following the scan until the birth of the fetus at the anterior portion of the external os; R^2 Linear < 0.001 (*p*=0.748) for 277 spontaneous births.

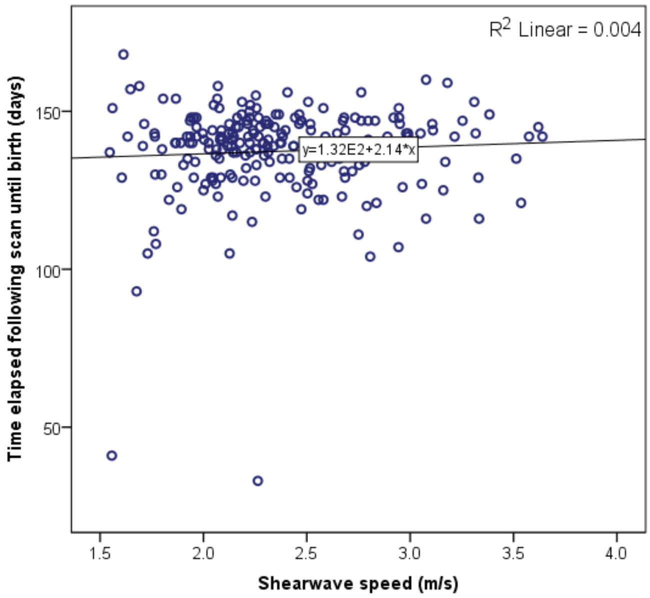


Figure 6.15: Correlation of shear wave speed to the time elapsed following the scan until the birth of the fetus at the posterior portion of the external os; R^2 Linear = 0.004 (p=0.343) for 277 spontaneous births.

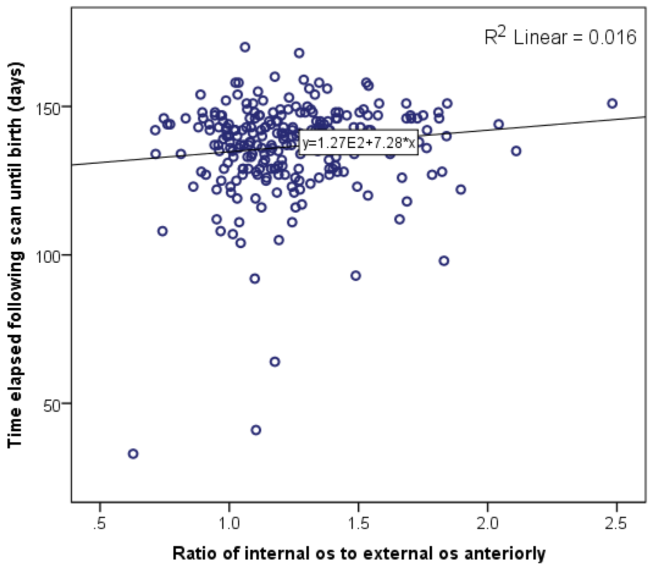


Figure 6.16: Correlation of the ratio of the internal os/external os in the anterior portion of the cervix to the time elapsed following the scan until the birth of the fetus; R^2 Linear = 0.016 (p=0.043) for 277 spontaneous births.

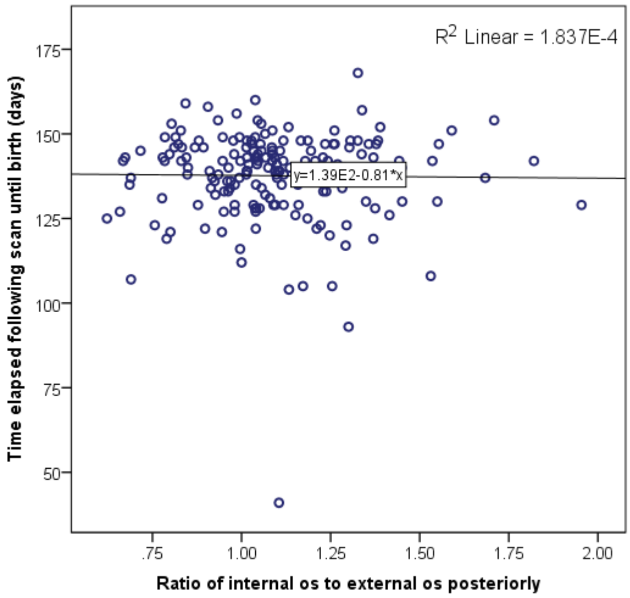


Figure 6.17: Correlation of the ratio of the internal os/external os in the posterior portion of the cervix to the time elapsed following the scan until the birth of the fetus; R^2 Linear <0.001 (p=0.343) for 277 spontaneous births.

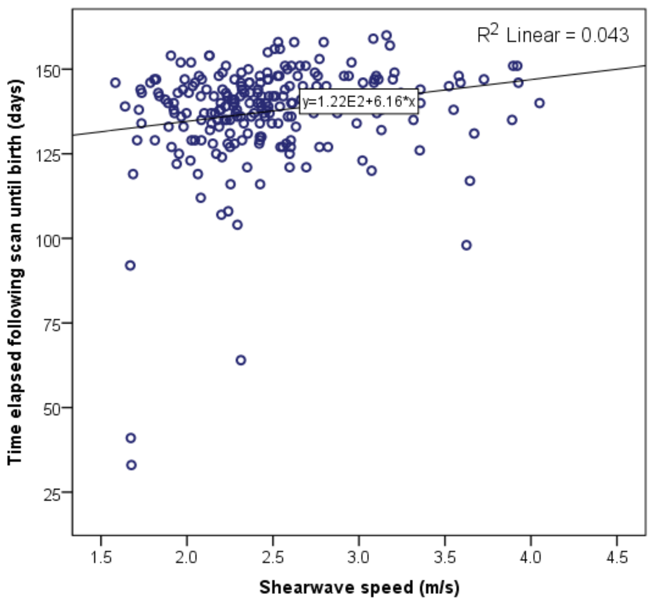


Figure 6.18: Correlation of shear wave speed to the time elapsed following the scan until the birth of the fetus at the anterior portion of the internal os; R^2 Linear = 0.043 (p=0.001) for 246 participants examined between 18 and 20+6 weeks of pregnancy undergoing spontaneous births.

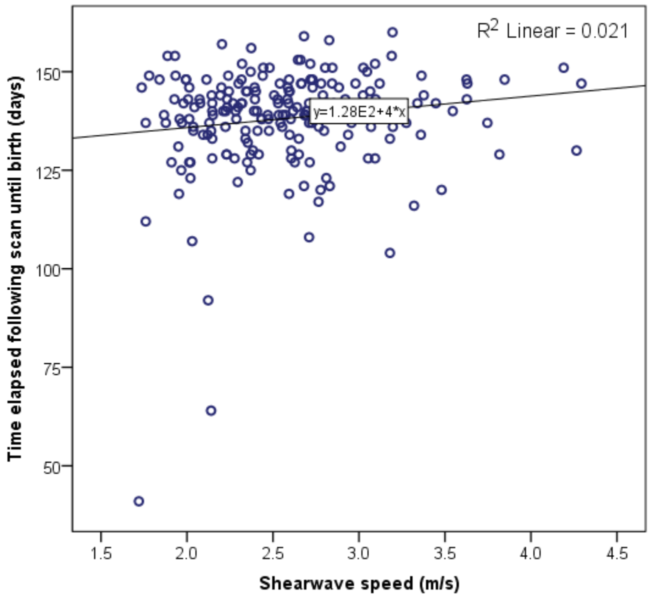


Figure 6.19: Correlation of shear wave speed to the time elapsed following the scan until the birth of the fetus at the posterior portion of the internal os; R^2 Linear = 0.021 (*p*=0.040) for 246 participants examined between 18 and 20+6 weeks of pregnancy undergoing spontaneous births.

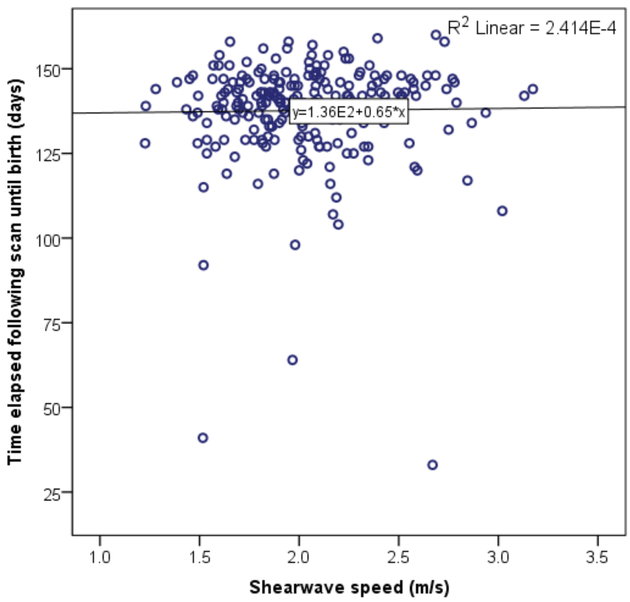


Figure 6.20: Correlation of shear wave speed to the time elapsed following the scan until the birth of the fetus at the anterior portion of the internal os; R^2 Linear < 0.001 (*p*=0.812) for 246 participants examined between 18 and 20+6 weeks of pregnancy undergoing spontaneous births.

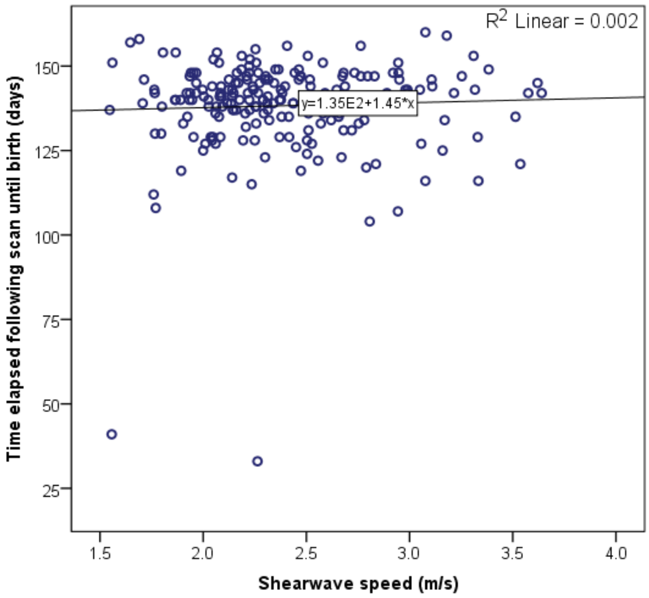


Figure 6.21: Correlation of shear wave speed to the time elapsed following the scan until the birth of the fetus at the posterior portion of the external os; R^2 Linear = 0.002 (*p*=0.527) for 246 participants examined between 18 and 20+6 weeks of pregnancy undergoing spontaneous births.

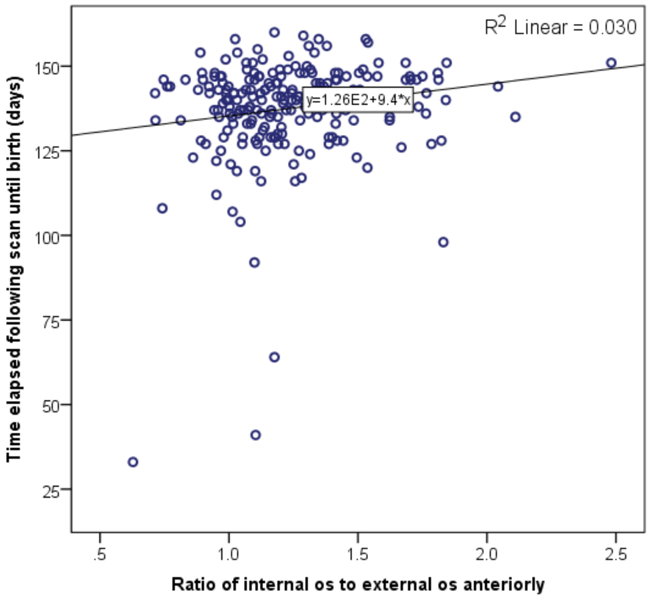


Figure 6.22: Correlation of the ratio of the internal os/external os in the anterior portion of the cervix to the time elapsed following the scan until the birth of the fetus; R^2 Linear = 0.030 (*p*=0.009) for 246 participants examined between 18 and 20+6 weeks of pregnancy undergoing spontaneous births.

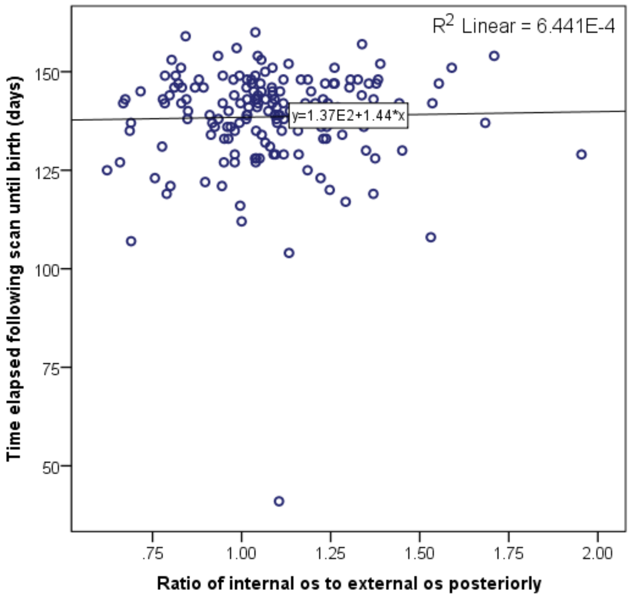


Figure 6.23: Correlation of the ratio of the internal os/external os in the posterior portion of the cervix to the time elapsed following the scan until the birth of the fetus; R^2 Linear < 0.001 (*p*=0.741) for 246 participants examined between 18 and 20+6 weeks of pregnancy undergoing spontaneous births.

6.4.2 Inter-operator testing

Inter-operator testing has been assessed on 15 of the participants. Due to reliable shear wave propagation being unobtainable in some regions, the number of comparisons that was possible in each region is as follows: 15 comparisons at the posterior and anterior portions of the external os, 14 at the anterior portion of the internal os and 6 at the posterior portion of the internal os. In each of the regions of the cervix the ICC obtained was as follows; Internal os Anterior: 0.97 (CI 0.90 - 0.99), Internal os Posterior: 0.60 (CI 0.24 - 0.87), External os Anterior: 0.91 (CI 0.73 - 0.97), External os Posterior: 0.95 (CI 0.82 - 0.98)

6.5 **Discussion**

This work has important findings. A non-invasive transabdominal shear wave elastography technique has been used, and a significant correlation of shear wave speed to time until delivery has been shown at the anterior portion of the internal os (Figures 6.2, 6.12) Whilst a significant increase in this correlation has been shown in women who were scanned between the 18th week and the end of the 20th week of pregnancy (Figure 6.18). In the posterior portion of the internal os shear wave speeds are also reduced in women who had a spontaneous preterm birth and there is a significant correlation to time to delivery for these women (Figure 6.13), and this correlation increases in significance in women who were scanned between the 18th and 20th week of pregnancy (Figure 6.19). Participants who subsequently delivered preterm had reduced shear wave speeds in these regions compared to patients who delivered at term, this effect being most apparent in the extreme to very preterm births. Importantly, a reduction in shear wave speed has been identified before the length of the cervix has shortened.

The graphs in Figures 6.8 and 6.9 demonstrate the trend of reduced shear wave speed in the preterm births and the increasing speed for term births at the anterior and posterior portions of the internal os for participants who delivered the fetus following spontaneous labour. This trend is less apparent in the posterior portion of the external os and not apparent in the anterior portion of the external os (Figures 6.10 and 6.11).

Using strain elastography and a transvaginal ultrasound approach, Swiatowska et al[27] found that a softening of the cervix in a cervix exhibiting a normal length increased the possibility of subsequent preterm birth. Using shear wave elastography technology and a transvaginal ultrasound approach, work by Hernandez et al[17] has shown that a reduction in shear wave speed between 18 to 24 weeks of pregnancy increases the risk of preterm birth. A softening of the cervix with a normal cervical length increased the risk of SPTB by 4.5 times.[17] Agarwal et al[20] used point shear wave elastography and a transabdominal ultrasound approach to acquire shear wave speeds at the anterior portion of the internal os on 30 patients in the third trimester of pregnancy. Patients who delivered prior to 37 weeks of pregnancy had significantly slower shear wave speeds than those who delivered at greater than 37 weeks of pregnancy.[20] A limitation of this finding is that standard management paradigms recommend that screening of the cervix for the identification of cervical insufficiency should be performed between 16 and 28 weeks of pregnancy to facilitate the use of interventions to reduce the likelihood of progression to cervical insufficiency.

Softening of the cervix prior to labour is known to commence at the internal os and this can be an extended process commencing some time before active labour.[3] The external os is the last portion of the cervix to soften[3] and this work has shown that the stiffness at the external os has not been predictive of subsequent preterm birth in both the anterior and posterior portions (Figures 6.4, 6.14, 6.20 and 6.5, 6.15, 6.21). The posterior portion of the internal os has shown a correlation between shear wave speeds and time until birth which is significant for the spontaneous births only (Figure 6.13 and 6.19); whilst this correlation is not as significant than at the anterior portion of the internal os, and this may be due to the posterior portion of the cervix producing less reliable shear wave propagation than the anterior portion.[28, 29]

A reduction in shear wave speed indicating softening of the cervix has been identified in late compared to early pregnancy,[18] with a gradual reduction in shear wave speed over the duration of pregnancy also identified.[30, 31] As the results of this work has shown (Table 6.1), there appears to be some variation in shear wave speed dependant on the weeks of pregnancy that the scan is performed at, age of the mother, ethnicity and previous number of pregnancies. This work has shown that particularly at the internal os the cervix has reach maximal stiffness between the 18th and 20th week of pregnancy with a gradual reduction in shear wave speed up until the 28th week. An increase in shear wave speed at the internal os has also been shown in women who have had greater than five pregnancies. The variation between different patient groups and the current variation in shear wave technology between ultrasound providers may mean that specific cut off values of shear wave speed below which the risk of preterm birth is increased would be dependent on the individual technology used.[32]

The internal os has been shown to be stiffer and produce faster shear wave speeds than the external os.[18, 33] This work has also shown that the internal os is stiffer than the external os during the mid-trimester in participants who deliver the fetus at over 37 weeks of pregnancy. In the participants who delivered prior to 28 weeks of pregnancy there has been a reduction in the speed of the shear wave registered at the internal compared to external os. This reduction in speed at the anterior portion of the internal os was less marked in the late preterm births. Unique to this work and also applicable to all technology and all women, a ratio has been calculated by dividing the shear wave speed acquired at the internal os by speed acquired at the external os in both the anterior and posterior regions of the cervix. Demonstrated in Figures 6.6 the ratio formulated at the anterior portion of the cervix has shown a significant correlation to time to delivery, and this correlation is improved when applied to the spontaneous births only (Figure 6.16); and this correlation increases to a greater significance when the participants have been examined between the 18th to the end of the 20th week of pregnancy (Figure 6.22). Table 6.3 also shows a ratio of less than one between the internal and external os in the anterior cervix for the women who delivered prior to 28 weeks of pregnancy. A ratio between the internal and external os at the posterior portion of the cervix has shown a poor correlation for all patient groups (Figures 6.7, 6.17 and 6.23).

This work has shown good reproducibility between sonographers with excellent correlation at the anterior portion of the internal os. At the external os, both the anterior and posterior portions also show excellent correlation between sonographers with a slightly larger confidence interval in both of these regions than at the anterior portion of the internal os. A moderate agreement has been obtained at the posterior portion of the internal os with a large confidence interval in this region.

This work has been limited by the low number of spontaneous preterm births in the data set and the use of one shear wave technology provider.

6.6 **Conclusion**

In conclusion, it appears that a non-invasive transabdominal technique can be used to identify a reduction in shear wave speeds in the internal os in the mid-trimester, particularly in the anterior portion of the cervix, in women who have a subsequent preterm birth. Importantly the reduction in speed has occurred before there has been a reduction in cervical length. A ratio of shear wave speed in the internal os over the external os in the anterior region of the cervix, can also be used as a predictive value for preterm birth, and is applicable to all patient groups and shear wave technologies.

6.7 **References**

1. Department of Health, The Women and Infants Research Foundation, The University of Western Australia, AMA, RANCOG, RACGP's. The Western Australian Preterm Prevention Initiative Western Australia: 2014.
2. Taylor BK. Sonographic Assessment of Cervical Length and the Risk of Preterm Birth. Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2011; 40(5):617-631.
3. Myers KM, Feltovich H, Mazza E, et al. The mechanical role of the cervix in pregnancy. J Biomech. 2015; 48(9):1511-23.
4. Retzke JD, Sonek JD, Lehmann J, Yazdi B, Kagan KO. Comparison of three methods of cervical measurement in the first trimester: Single-line, two-line, and tracing. Prenatal Diagnosis. 2013; 33(3):262-268.

5. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol. 2012; 206(2):124.e1-124.e19.

6. Cutchie W. Cervical shortening and cervical insufficiency [Internet]. http://3centres.com.au/guidelines/complications-in-pregnancy-and-birth/cervical-shortening-and-cervical-insufficiency. Accessed: 30 August 2012.

7. Di Tommaso M, Berghella V. Cervical length for the prediction and prevention of preterm birth. Expert Review of Obstetrics and Gynecology. 2013; 8(4):345-355.

8. Olson Chen C. Ultrasound for cervical length. Ultrasound clinics. 2013; 8(1):1-11.

9. Iams JD, Goldenberg RL, Mercer BM, et al. The Preterm Prediction Study: Can low-risk women destined for spontaneous preterm birth be identified? Am J Obstet Gynecol. 2001; 184(4):652-655.

10. To MS, Skentou CA, Royston P, Yu CKH, Nicolaides KH. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. Ultrasound in Obstetrics and Gynecology. 2006; 27(4):362-367.

11. Berghella V, Roman A, Daskalakis C, Ness A, Baxter JK. Gestational age at cervical length measurement and incidence of preterm birth. Obstet Gynecol. 2007; 110(2 I):311-317.

12. Nott JP, Bonney EA, Pickering JD, Simpson NAB. The structure and function of the cervix during pregnancy. Translational Research in Anatomy. 2016; 2:1-7.

13. Vink JY, Qin S, Brock CO, et al. A new paradigm for the role of smooth muscle cells in the human cervix. American journal of obstetrics and gynecology. 2016; 215(4):478.

14. Myers KM, Socrate S, Paskaleva A, House M. A study of the anisotropy and tension/compression behavior of human cervical tissue. J Biomech Eng. 2010; 132(2):021003.

15. Lim K, Butt K, Crane JM. SOGC Clinical Practice Guideline. Ultrasonographic cervical length assessment in predicting preterm birth in singleton pregnancies. J Obstet Gynaecol Can [Practice Guideline]. 2011; 33(5):486-99.

16. Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. Journal of the Acoustical Society of America. 2001; 110(1):625-634.

17. Hernandez-Andrade E, Maymon E, Luewan S, et al. A soft cervix, categorized by shear-wave elastography, in women with short or with normal cervical length at 18-24 weeks is associated with a higher prevalence of spontaneous preterm delivery. J Perinat Med. 2018; 46(5):489-501.

18. Carlson LC, Hall TJ, Rosado-Mendez IM, Palmeri ML, Feltovich H. Detection of Changes in Cervical Softness Using Shear Wave Speed in Early versus Late Pregnancy: An in Vivo Cross-Sectional Study. Ultrasound in medicine & biology. 2018; 44(3):515-521.

19. Muller M, Aït-Belkacem D, Hessabi M, et al. Assessment of the Cervix in Pregnant Women Using Shear Wave Elastography: A Feasibility Study. Ultrasound in Medicine & Biology. 2015; 41(11):2789-2797.

20. Agarwal S, Agarwal A, Joon P, Saraswat S, Chandak S. Fetal adrenal gland biometry and cervical elastography as predictors of preterm birth: A comparative study. Ultrasound (Leeds, England). 2018; 26(1):54-62.

21. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists(RANZCOG), College Statements and Guidelines, Measurement of cervical length for prediction of preterm birth 2017.

22. Thiele M, Detlefsen S, Sevelsted Moller L, et al. Transient and 2-Dimensional Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver Fibrosis and Cirrhosis. Gastroenterology. 2016; 150(1):123-33.

23. O'Hara S, Zelesco M, Sun Z. Shear wave elastography of the maternal cervix: A transabdominal technique. Australasian Journal of Ultrasound in Medicine. 2019; 22(2):96-103.

24. O'Hara S, Zelesco M, Rocke K, Stevenson G, Sun Z. Reliability Indicators for 2-Dimensional Shear Wave Elastography. Journal of Ultrasound in Medicine. 2019; 38(11):3065-3071.

25. Fleiss JL, Cohen J. The Equivalence of Weighted Kappa and the Intraclass Correlation Coefficient as Measures of Reliability. Educational and Psychological Measurement. 1973; 33(3):613-619.

26. Rankin G, Stokes M. Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. Clinical Rehabilitation. 1998; 12(3):187-199.

27. Swiatkowska-Freund M, Preis K. Elastography of the uterine cervix: implications for success of induction of labor. Ultrasound Obstet Gynecol. 2011; 38(1):52-56.

28. O'Hara S, Zelesco M, Sun Z. Shear wave elastography of the maternal cervix: A transabdominal technique. Australasian Journal of Ultrasound in Medicine. 2018; 22(2):96-103.

29. O'Hara S, Zelesco M, Sun Z. Shear Wave Elastography on the Uterine Cervix: Technical Development for the Transvaginal Approach. J Ultrasound Med. 2019; 38(4):1049-1060.

30. Peralta L, Molina FS, Melchor J, et al. Transient Elastography to Assess the Cervical Ripening during Pregnancy: A Preliminary Study. Ultraschall in Med. 2017; 38(04):395-402.

31. Ono T, Katsura D, Yamada K, et al. Use of ultrasound shear-wave elastography to evaluate change in cervical stiffness during pregnancy. J Obstet Gynaecol Res. 2017; 43(9):1405-1410.

32. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. Ultrasound Med Biol. 2015; 41(5):1126-47.

33. Palmeri M, Feltovich H, Homyk A, Carlson L, Hall T. Evaluating the feasibility of acoustic radiation force impulse shear wave elasticity imaging of the uterine cervix with an intracavity array: a simulation study. Ultrasonics, Ferroelectrics, and Frequency Control, IEEE Transactions on. 2013; 60(10):2053-2064.

Chapter 7

Conclusions and Future Directions

7.1 Conclusions

The study undertaken in this project has investigated the used of two dimensional (2D) shear wave elastography in biological tissues and its application in assessing the strength of the cervix in non-gravid and gravid women. This work has further developed the body of knowledge on the use of shear wave elastography in biological tissues and its application to the cervix.

This research has assessed the reliability of 2D shear wave elastography for use in biological tissues, and the impact of the standard deviation on the mean shear wave speed obtained. The outcomes of this are summarised as follows:

- Reliability of shear wave speeds obtained is affected by a number of ultrasound artifacts
- Reliability indicators provided by the ultrasound technology providers should be utilised
- The standard deviation of the values obtained in the region of interest is an important indicator of shear wave reliability and should be considered by the sonographer

The transvaginal ultrasound technique has been investigated and developed on non-gravid women. The technique development for the transvaginal ultrasound approach using shear wave elastography on the maternal cervix has added to the body of evidence available for this work. This has advanced the use of this technique and uncovered pitfalls that the sonographer needs to be aware of in the use of this technology. The outcomes of this are summarised as follows:

- Transducer pressure can produce a localised pre-stress in the cervix and result in higher shear wave speeds being obtained, and due to this transducer pressure should be kept to a minimum whilst still maintaining a good B-mode window
- There appears to be minimal difference in shear wave speeds obtained in women dependant on previous vaginal, or c-section births and also between ethnicities
- The internal os produces faster shear wave speeds than the external os and this supports the theory that the internal os has a sphincter like effect to maintain the product of menses prior to evacuation, and the maintenance of the fetus in pregnancy
- Reliable shear wave speeds are more likely to be obtained in the anterior portion of the cervix
- The depth of interrogation to the posterior portions of the cervix appears to be problematic for reliable shear wave production in this region
- The depth of interrogation to the internal os, in particular the posterior portion, results in the least number of reliable shear wave speeds being obtained in this region
- The posterior portion of the cervix produces higher shear wave speeds than the anterior portion in the transvaginal approach

- The positon of the cervix affects the likelihood of shear waves being produced, and anisotropy of the tissues in the collagen and muscular layers of the cervix may be contributing to this
- Attenuation properties of the cervix and shear wave artifacts appear to reduce the number of reliable shear wave measurements obtained deep to the cervical canal
- The posterior and anterior portions of both the internal and external os should be interrogated individually and a small elastogram size for each region of interest should be used, with the use of a large elastogram over the entire cervix discouraged
- The ideal position of the cervix to obtain shear wave measurements is with the cervical canal in a horizontal position

This research has developed a novel transabdominal ultrasound technique for assessing the maternal cervix, and shown that it is possible for reliable propagation of the shear wave to be produced deep to fluid filled structures that do not contain any particulate. The outcomes of this are summarised as follows:

- Shear wave movement cannot be produced in fluid, but the main ARFI pulses can be transmitted through echo free fluid filled structures to produce shear waves in a structure deep to the fluid
- Shear wave speeds obtained in an ultrasound phantom have been shown to be the same with direct contact on the phantom with the ultrasound transducer and also through a saline filled water bath
- It is possible to produce reliable shear waves in the maternal cervix deep to a moderately filled maternal bladder

- Using the transabdominal ultrasound approach a greater number of reliable shear wave speed measurements are obtained in the anterior portion of the cervix compared to the posterior
- It appears that the increased depth to the posterior portion of the cervix from the transducer face is affecting the production of reliable shear waves in this region
- The posterior portion of the external os produced shear wave speeds that were significantly greater than the anterior portion of the external os, with no differences at the internal os
- The internal os produced higher shear wave speeds than the external os
- Accurate shear wave measurements can be obtained in most patients in the anterior cervix with a reduced number obtained in posterior cervix

The differences between the transvaginal and transabdominal ultrasound approaches for obtaining shear wave speeds in the maternal cervix has also been investigated. The outcomes of this are summarised as follows:

- The anterior portion of the cervix produces a greater number of reliable shear wave speeds than the posterior in both transabdominal and transvaginal ultrasound approaches
- The posterior portion of the internal os produces the lowest number of reliable shear wave measurement in both approaches
- Depth of transmission to the posterior portion of the cervix is problematic in both ultrasound approaches

- Both approaches produce higher shear wave speeds at the internal os compared to the external os
- Both approaches produce higher shear wave speeds posteriorly compared to anteriorly
- There are differences in shear wave speeds obtained between the transabdominal and transvaginal ultrasound approaches, with the largest differences at the internal os
- The transvaginal ultrasound approach produces faster shear wave speeds than the transabdominal approach at the internal os
- The differences in shear wave speeds obtained between both approaches was minimal at the external os with insignificant differences produced both anteriorly and posteriorly
- Even though it is possible to use both techniques we have shown that the speeds obtained in the transvaginal approach are different than in the transabdominal approach, particularly in the internal os, and the speeds obtained would need to be assessed independently

Finally, this research has also shown that by using a transabdominal ultrasound approach to obtain 2D shear wave elastography measurements in the mid-trimester of pregnancy, it may be possible to determine which women are at a greater possibility of preterm birth due to a reduction in shear wave speeds. The outcomes of this are summarised as follows:

- The non-invasive transabdominal technique has shown a significant correlation between the shear wave speed obtained at the anterior portion of the internal os and the time to delivery
- The shear wave speed at the anterior portion of the internal os is slower in women who deliver preterm compared to women who deliver term, particularly in extremely preterm births
- A reduction in shear wave speed at the anterior portion of the internal os has been identified before shortening of the cervical length has occurred
- The posterior portion of the internal os shows a significant correlation between shear wave speed and the time until birth for women who gave birth spontaneously and in particular presented between the 18^{th} and the end of the 20^{th} week for their ultrasound examination
- The posterior and anterior portions of the external os showed a poor correlation between the shear wave speeds obtained and the time until delivery
- Some variation in shear wave speeds obtained in pregnancy has been identified depending on the weeks of pregnancy at the time of the scan, the age of the mother, ethnicity and number of prior pregnancies
- A ratio formulated of the shear wave speed obtained at the internal os over the external os, has shown a significant correlation between the ratio and the time elapsed to birth of the fetus for the anterior portion of the cervix
- This ratio could be applied to all patient groups and differing shear wave technologies

7.2 **Future Directions**

This study improves our knowledge of 2D shear wave elastography and its use in biological tissues. This work highlights the use of a non-invasive transabdominal ultrasound approach to identify women who are at an increased risk of preterm birth. This work has been limited by the low preterm birth rate in the data set. The correlation of shear wave speed and time to deliver of the fetus whilst significant at the anterior and posterior portions of the internal os, also identifies a number of cases whereby there was a reduction in shear wave speeds in participants who gave birth at term. Even though an overall trend of reduced shear wave speeds in patients who have given birth preterm compared to term has been identified, the low number of early preterm births limits the usefulness of these results. Most of the women who gave birth preterm delivered the fetus between the 34^{th} and 37^{th} week of pregnancy, and the mean shear wave speed in these participants is very similar to the participants who gave birth in the 37^{th} week or term of pregnancy. The use of one technology provider and the current inconsistencies between technology providers limits the findings of this research.

Suggestions for future research are as follows:

- Follow up of participants.
- Future work could assess the use of 2D shear wave elastography on the maternal cervix in women who have been identified as being at increased risk of preterm birth due to medical factors and attending a tertiary centre.

- A larger cross sectional group of patients from both low and high risk groups should yield a greater number of patients who undergo a subsequent preterm birth, and thus a greater participation rate would add strength to the results obtained.
- A further direction would be to attempt to replicate this work with a multi-centred approach. This would allow the acquisition of shear wave speeds on the maternal cervix across a greater variation of sonographer expertise, and across different technology providers.

Appendix I: Statements of contribution of others

Statement of contribution of others to (Reliability indicators for the use of two dimensional shear wave elastography)

O'Hara S, Zelesco M, Rocke K, Stevenson G, Sun Z. Reliability Indicators for 2-Dimensional Shear Wave Elastography. Journal of Ultrasound in Medicine. 2019; 38(11):3065-3071. doi:10.1002/jum.14984.

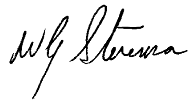
To whom it may concern

I, Sandra O’Hara contributed (I designed the paper, collected the data and images used and wrote the manuscript) to the paper (Reliability indicators for the use of two dimensional shear wave elastography)

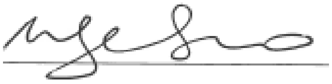
Sandra O’Hara

I, as a Co-Author, endorse that this level of contribution by the candidate indicated above is appropriate

Karen Rocke



Gil Stevenson



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Expected size (number of pages)	250
Requestor Location	Curtin University Kent St Bentley, Ms. 6102 Australia Attn: Curtin University
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Reliability Indicators for 2-Dimensional Shear Wave Elastography

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Ultrasound (US) shear wave technology providers have either point shear wave elastography (SWE) or 2-dimensional SWE available on their US systems. With 2-dimensional SWE, larger regions of interest can be interrogated, with both the main acoustic radiation pulses and the resultant shear waves potentially being affected by US artifacts. Some providers assist the operator with elastographic maps indicating the reliability or precision of the shear wave propagation. This Technical Innovation explores the importance of the consideration of the precision maps and standard deviation output available on some devices and the implications for conversion of shear wave speed to pressure.

Key Words—reliability; shear wave elastography; 2-dimensional; ultrasound

Approval for use of the US imaging in this article was obtained from the SKG Radiology Institutional Review Board.

Shear wave elastography (SWE) uses ultrasound (US) technology to quantify the stiffness of tissues in the region being assessed. The basic premise is that the US pulse used in B-mode imaging is modified to become a low-frequency/high-intensity push pulse often called an acoustic radiation force impulse.[1] This acoustic radiation force impulse produces small tissue movements in the plane of the push pulse, which creates shear waves that move in a sideways direction away from the push pulse.[1] The momentum of the push pulse is transferred to the tissues, causing a propagation of the shear wave through the medium by way of attenuation mechanisms such as absorption and scattering.[2] The speed of shear wave movement is slow compared to the speed of the US pulses, and this movement can be tracked by the US machine.[3] The movement of the shear wave is tracked by tracking pulses in a similar method as Doppler technology, with US vendors using different methods to determine the shear wave arrival time.[2,4] A typical time-of-flight method is to estimate the speed of the shear wave arrival time at positions lateral to the region of excitation created by the push pulse. A linear regression of time versus the position of the data within a kernel is performed to determine the shear wave speed (SWS).[2]

Relative stiffness of the tissue is quantified in two ways. The SWS obtained in meters per second is the "raw" data and indicates the speed of shear wave propagation; this can be mathematically converted to a measure of tissue elasticity output in kilopascals.[1] Most shear wave technology providers convert the SWS to kilopascals using the Young modulus equation: kPa = speed^2 $\times$ 3.[5] The conversion of SWS to kilopascals makes the assumption that the

Received January 29, 2019, from SKG Radiology, Subiaco, Perth, Western Australia, Australia (S.O., K.R.); Discipline of Medical Radiation Sciences, School of Molecular and Life Sciences, Curtin University, Perth, Western Australia, Australia (S.O., Z.S.); Department of Medical Imaging, Fiona Stanley Hospital, Murdoch, Western Australia, Australia (M.Z.); and Real Statistics, Bangor, County Down, Northern Ireland (G.S.). Manuscript accepted for publication February 14, 2019.

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Abbreviations

ROI, region of interest; SD, standard deviation; SWE, shear wave elastography; SWS, shear wave speed; US, ultrasound

doi:10.1002/jum.14984

region being interrogated is isotropic and homogeneous and has linear behavior; hence, the operator should be aware that biological tissues may break the assumptions used in this calculation.[5]

Point SWE technology investigates regions of tissue whereby one or two push pulses are used to produce shear waves in a small and fixed region of interest (ROI).[5] Many US vendors now provide 2-dimensional (2D) SWE technology, which differs from point SWE in a number of ways. Larger ROIs can be interrogated by using 2D SWE. As can be seen in Figure 1, in 2D SWE, a color elastographic box can be placed over a larger region of tissue. The color of the elastogram is a qualitative representation of the tissue stiffness, and it is possible to place multiple ROIs within the elastogram to obtain the quantitative measurements of the SWS or tissue elasticity. A recent update to the guidelines on the use of elastography from the World Federation for Ultrasound in Medicine and Biology recommended that a single ROI be placed per elastogram.[6] To achieve the larger elastogram used in 2D SWE, multiple push pulses and tracking pulses are being applied at finite distances across the elastogram. Some vendors focus the push and tracking pulses at a specified depth into the elastogram, whereas others such as SuperSonic shear imaging (SuperSonic Imagine, Aix-en-Provence, France) push multiple pulses down each line of sight to produce a Mach cone effect throughout the elastogram.[1]

Reliability of SWE

An assumption of the time-of-flight tracking methods used to estimate SWS is that the tissue in the ROI is homogeneous.[2] In soft tissues, this assumption of homogeneity can be violated, creating speed artifacts.[2] The precision or reliability of the shear wave propagation can be affected by a number of factors. The transmission of the main pushing pulses can be affected by the strength of the pulse and variation in tissue density and can be prone to acoustic attenuation, absorption, reflection, and scatter. Shear wave production can also be affected by scatter, reflection, refraction, and anisotropic tissues, resulting in errors in SWS estimation.[5] The larger elastogram in 2D SWE uses multiple push pulses across the elastogram over larger regions of tissue, and there may be tissue inconsistencies across the region of the elastogram and also in the elevation plane of the transducer that can affect the speed of shear wave propagation.[4] Shear wave speed measurements can also be affected by random errors such as jitter in the displacement tracking of the US device.[4]

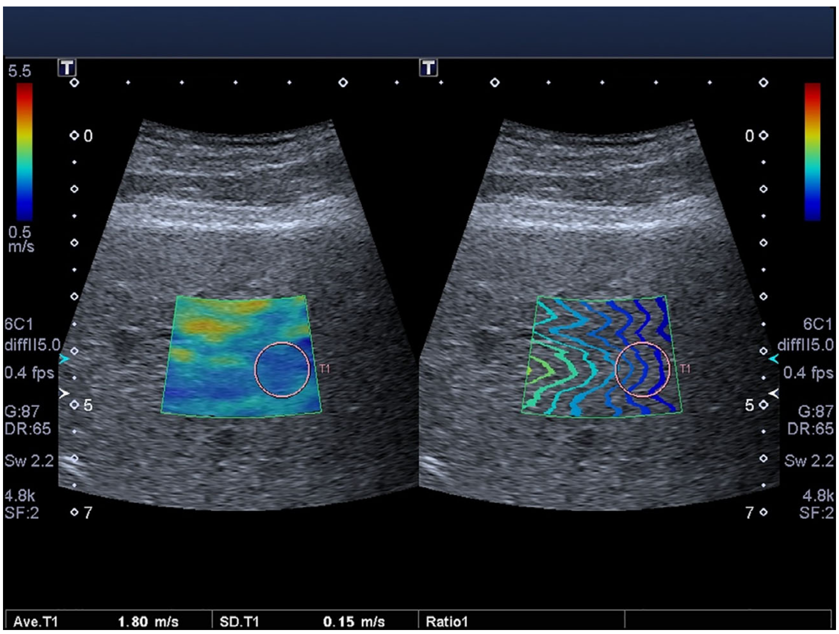


Figure 1. Two-dimensional SWE elastogram placed in the right lobe of the liver showing an elastogram and propagation map, with a mean speed of 1.80 m/s and an SD of 0.15 m/s at region T1.

Two-dimensional SWE technology providers supply the operator with indications of the reliability of shear wave propagation unique to each vendor. The GE Healthcare (Chicago, IL) system recommends that the color elastogram box should have greater than 50% of color filling for shear wave propagation to be considered reliable. The Epiq system (Philips Healthcare, Bothell, WA) uses a confidence map, and Siemens Medical Solutions (Mountain View, CA) technology a quality map, whereby red regions are considered to have unreliable values, green regions the most accurate, and yellow regions less than optimal. The Canon Medical (Otawara-shi, Japan) technology uses wave front maps to indicate the reliability of shear wave propagation, with parallel equidistant lines indicating reliable shear wave propagation.[3] The propagation map on the Canon device also gives an indication of the speed of shear wave propagation. The closer the lines are together, the slower the SWS, with a greater distance between and widening of the lines indicating faster SWS.

It has been recommended that a 10-mm ROI be used to acquire the mean speed or kilopascals for the assessment of liver stiffness.[3] Within the 10-mm ROI, many values of the speed of shear wave propagation are being obtained, and the mean speed is displayed. The numerous values of SWS obtained are mathematically converted to a kilopascal value, and the mean kilopascal value can be displayed on elasticity elastogram maps. Most 2D SWE providers also display the standard deviation (SD) of the values obtained within the ROI, with SuperSonic shear imaging technology also displaying the minimum and maximum values registered within the data set.

The fact that a mean (or average) value of SWS is quoted indicates immediately that not all of the measured values of SWS are the same, that there is a level of variation between these values, and that an average value provides an indication of where the collection of values is generally located on the scale of SWS. In the context of a perfect measuring instrument making multiple measurements of an inanimate object maintained in a constant environment, then, whether 10 measurements or 10,000 measurements were taken, there would be an expectation that all of those values would be identical; however, this is rarely the case. Not all of these values will be identical, so account needs to be taken of the extent of variation or scatter that is present in the set of measurements. The formal name for this is the variance. It is calculated by expressing the distance each individual is from the mean value (ie, as a deviation from the mean = value − mean), squaring those deviations (because values smaller than the mean will produce negative deviations, and values larger than the mean will produce positive deviations), adding them all together, and calculating an average. The square root of this variance is the SD. In other words, it is the root mean squared deviation about the mean. The SD quantifies the amount of scatter or dispersion present in a set of values; the larger the SD, the greater the scatter, and the smaller the SD, the less the scatter. The perfect instrument above would produce an SD of 0. Fisher's information is inversely proportional to variance[7]: the smaller the variance, the better the information.

Thus, the SD can give the operator a further indication of the reliability of shear wave propagation. The Canon 2D SWE technology can be used as an example: a recommendation from Canon is that nearly 1000 values of speed are obtained from a 10-mm circular ROI, and the mean and SD of these values are displayed. Regions within the elastogram that have the most uniform color will be concordant with regions within the wave front map showing the straightest, most parallel, and equidistant propagation lines. These regions will also output the lowest SD. Regions of nonuniform color and distortion of propagation lines are indicative of artifacts affecting reliable shear wave propagation, resulting in unreliable SWSs. These regions also have a high SD. As can be seen in Figure 2, the T1 ROI has a uniform elastogram and wave front map and registers a mean speed of 1.70 m/s with an SD of 0.12 m/s. Adjacent to this, the T2 ROI has been placed in a region of nonprecise shear wave propagation indicated by the nonuniform elastogram and erratic wave front map. The distance between the wave front lines is also increased in this region, and an increased mean speed of 2.98 m/s and a much higher SD of 0.66 m/s has been obtained.

Although unlikely to occur, if as an example we make a strong assumption that a symmetric (normal) distribution of the nearly 1000 values obtained within a 10-mm ROI has been achieved, the mean, median, and mode values for the data set will be identical or very similar, with a symmetric spread of speeds around these central values. As illustrated in Figure 3, if the mean speed obtained is 1.5 m/s with an SD of 0.05

(3% of the mean), the central 68% of the speed values obtained (mean ± 1 SD) will range between 1.45 and 1.55 m/s, and 99.865% of the values (mean ± 3 SD) will range between 1.35 and 1.65 m/s, showing a very narrow range of values for the entire data set and high reliability for the mean. If the SD were 0.5 (33% of the mean), then the central 68% of values would range between 1.0 and 2.0 m/s, and 99.865% of our values would be ranging between 0 and 3 m/s. Thus, a high SD is indicative of a large variation of SWE speed values being obtained within the ROI, and the central mean value becomes less reliable as an indicator of tissue stiffness in this region because of the large variation of speeds being obtained.

The calculation of probable ranges outlined above depends principally on two assumptions: namely, independence between observations and conformity with the normal distribution. Independence implies that the value of any single observation could not

Figure 3. Illustration of a normal or symmetric distribution of values in a data set of 10,000 values with a mean value of 1.5 and an SD of 0.05.

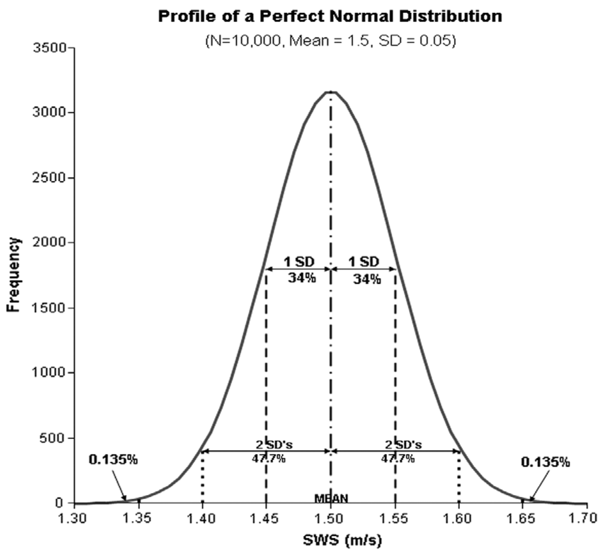
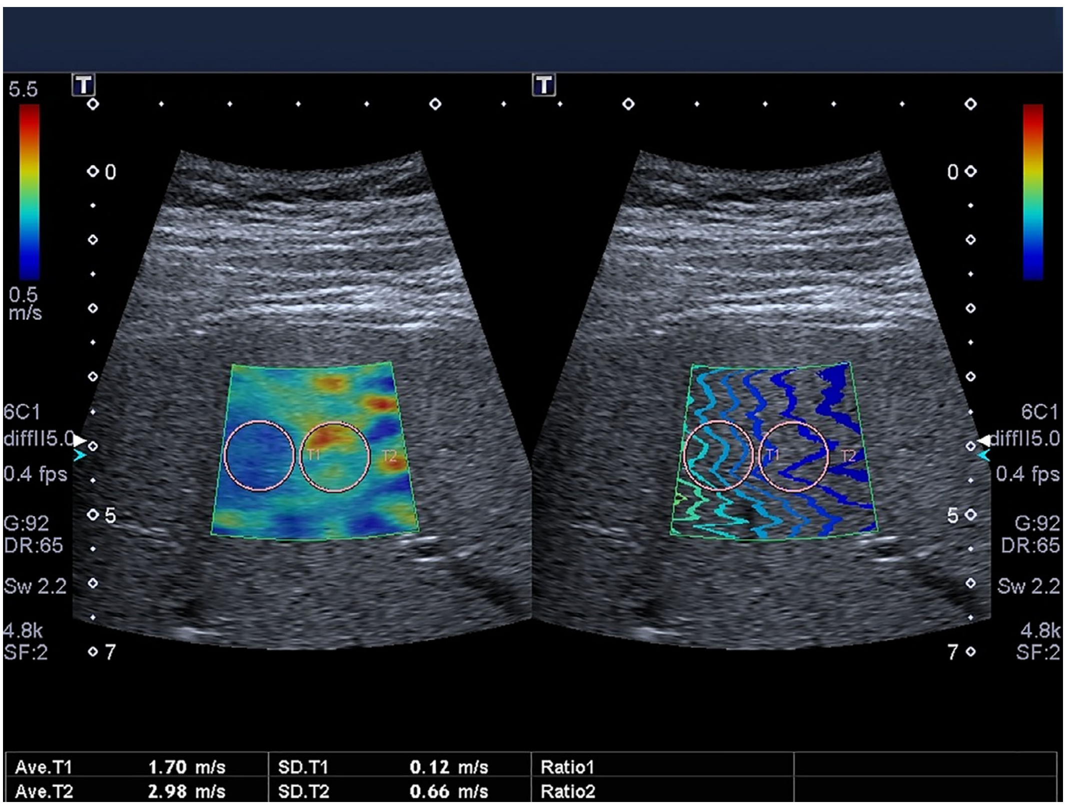


Figure 2. Two-dimensional SWE elastogram shown in a region of the liver with a uniform propagation map and elastogram at T1 with a mean speed of 1.70 m/s and an SD of 0.12 m/s and a nonuniform propagation map and elastogram at T2 with a mean speed of 2.98 m/s and an SD of 0.66 m/s.



affect, nor have been affected by, the value of any other observation. Given that a set of SWS values is sourced from the same liver in the same patient by the same machine in a single session over a short time, then the independence requirement cannot be met, leading to levels of variation that are likely to be less than would otherwise have been. Consequently, any range defined by mean $\pm$ n SDs will produce a fraction that will be slightly smaller than its normal equivalent. This should not deter the consideration and use of such fractions because, within the current context, it is expected that the associated underevaluation will be consistent and so remain useful as a guide for operators.

Conformity with the normal implies the property of symmetry. In statistical parlance, this is the coefficient of skewness and has a value of 0 if the distribution is symmetric about the mean. This is unlikely to be the case when the mean SWS has a low value, say 0.1 for illustration purposes. If the SD is 0.05, as before, then the deviate (mean – 2 SDs) corresponds to an SWS of $0.1 - 2 \times 0.05 = 0$, implying that 97.7% of the SWS values are greater than 0, and the remaining 2.3% are less than 0. Also, the deviate (mean – 3 SDs) corresponds to an SWS of $0.1 - 3 \times 0.05 = -0.05$.

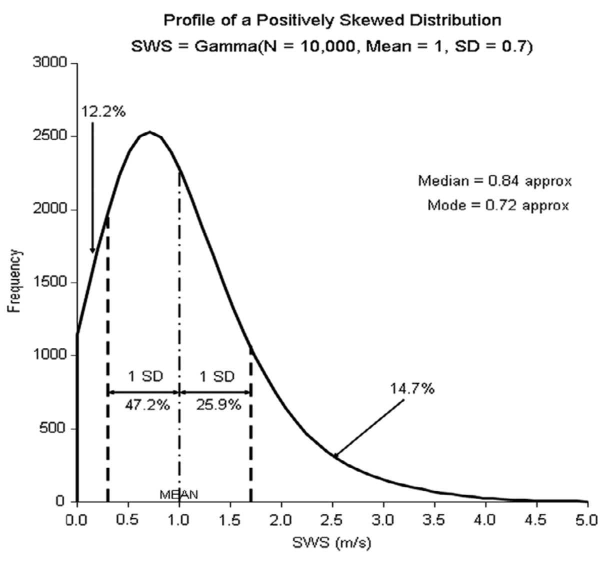
Theoretically the normal distribution ranges from $-\infty$ to $+\infty$, but speeds cannot be negative. Consequently, for SWS distributions, 0 m/s constitutes a lower domain boundary, and 100% of all SWS values will be greater than 0 (ignoring the exact value of 0, corresponding to total acoustic impedance.) With this "out-of-bounds" zone at the left end of the distribution, the only "room" for expansion of the range of values is at the right or high end of the distribution. Consequently, the distribution will become asymmetric, showing a long tail to the right, known as positive skewness, and will no longer be normal. In a positively skewed data set, the mean will be different from the median and mode values, and this will invalidate the use of the $\pm$ symbol as used in the above examples. If the skewness is only slightly positive, then, for all practical purposes, the normal method would probably suffice. If not, then the data would be better described by the gamma distribution. This is commonly used in the distributions of rates (and speed is a rate) where negative values are not possible.[8] However, computations involving the gamma distribution are considerably less "rule of thumb" than the normal. See Figure 4 for comparison. The mean, median, and mode are no longer coincident, and the same ordinates (at mean – SD and at mean + SD) now account for different (and unequal) proportions of the population of values.

In practice, two phenomena have been observed when undertaking liver SWE examinations. It can be observed that adjacent regions in the same patient may have differing values of SD but still return a similar mean speed. Regions with a nonuniform elastogram color, an erratic wave front map, and a higher SD have also been observed to have a much higher mean SWS than adjacent regions, as can be seen in Figure 2, with a widening of the distance between the wave front lines also being observed in this region. To this end, we have created scatterplots of the mean SWS and the SD for each value obtained on 6 patients undergoing liver assessments (Figure 5). All measurements were acquired with the Canon Aplio 500 shear wave technology. These scatterplots show an overall trend of an increasing SWS with an increasing SD for each participant, with some patients having a similar mean speed with an increasing SD.

Conversion of Speed to Pressure

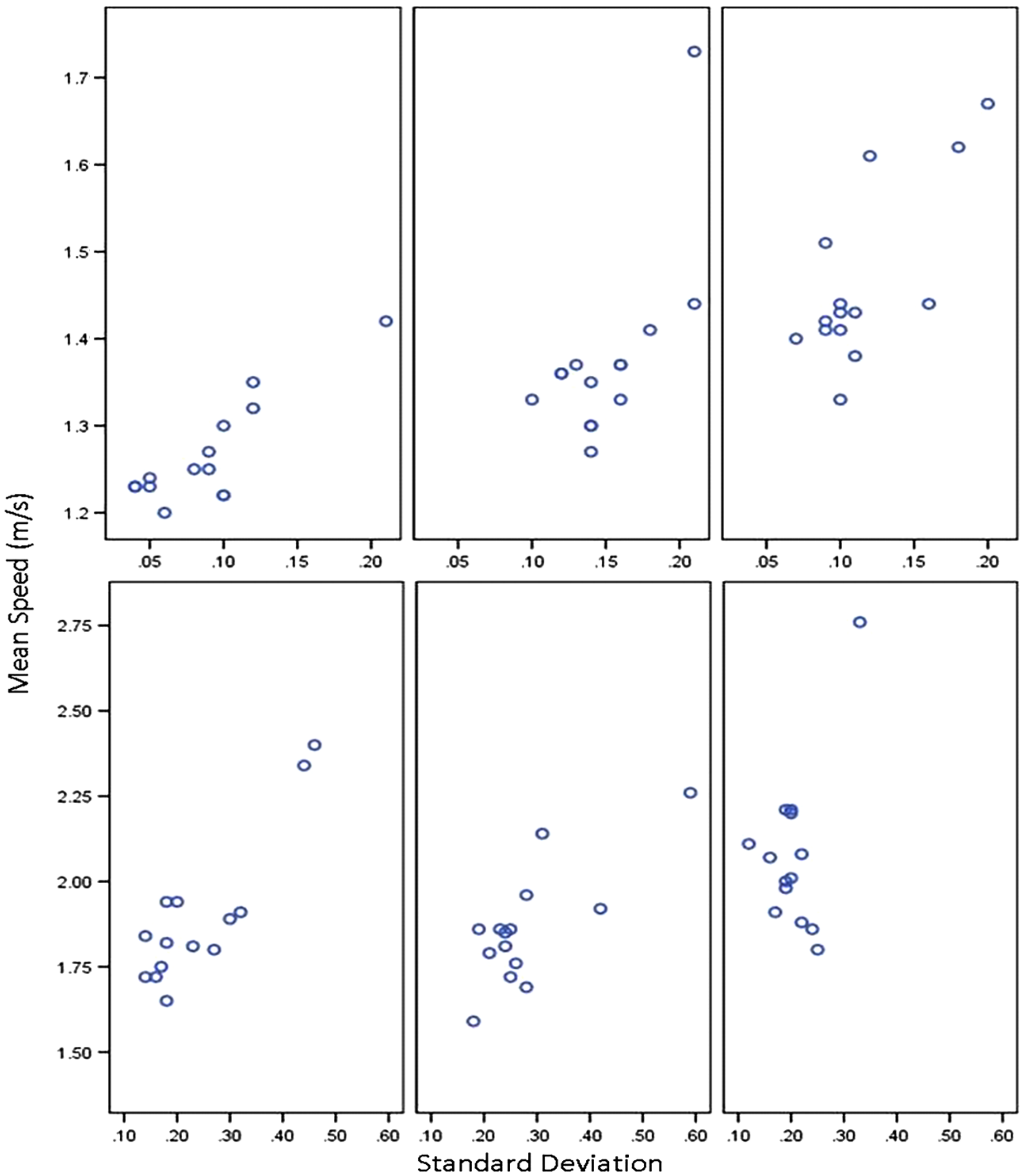
Consideration of the SD is also important for the conversion of the SWS in meters per second to elasticity

Figure 4. Example of a skewed distribution. The mean, median, and mode are no longer coincident, and the same ordinates (at mean – SD and mean + SD) now account for different (and unequal) proportions of the population of values.



in kilopascals. As shown in Figure 6, a mean speed of 1.36 m/s with an SD of 0.12 m/s has been obtained. The elasticity value calculated by the US machine is shown to be 5.4 kPa. If we convert the mean speed of 1.36 m/s to kilopascals using the mathematical conversion of speed$^2 \times 3$,[1] the value will be 5.5 kPa. This small difference can be explained by the fact that the nearly 1000 values of SWS in a 10-mm ROI are all being converted to kilopascals before a mean value is calculated, and as this range of values as signified by the SD reading is quite small, the values are minimally different from a mathematical conversion of the mean value alone. Observing the values in Figure 7, the mean SWS of 1.36 m/s has also been obtained but with a large SD of 0.94; thus, as explained previously, a much greater range of SWS values has been obtained in the

Figure 5. Scatterplots showing the mean speed and SD obtained for each value for 6 patients undergoing SWE of the liver.



ROI. The transformation of this larger range of SWS values to kilopascals has resulted in a value of 10.3 kPa. The resultant values would have different outcomes for the patient with the SWS value of 1.36 m/s, which is considered to be in the normal range for liver stiffness, with the value of 10.3 kPa being at a level of significant fibrosis.

When using the Canon shear wave technology, it has been recommended that the value of the SD be kept to less than 20% of the mean speed. Researchers at the Royal Melbourne Hospital have found that an SD that was greater than 15% of the mean speed showed low reliability and deviated by significant amounts from the median value obtained for the diagnosis of liver fibrosis.[9] This percentage of the SD to the mean of the SWS does not have a linear correlation with the SD obtained when these values are converted to kilopascals. As can be observed in Figure 4, the value of 1.36 m/s with an SD of 0.12 m/s, the SD equates to approximately 9% of the mean value. The conversion to kilopascals has a mean of 5.4 kPa and an SD of 1 kPa, with the SD now equating to 18% of the mean value. Thus, the consideration of obtaining a low SD in 2D SWE imaging is most relevant when obtaining the SWS.

Figure 6. Shear wave elastographic report page showing 5 SWS values and the calculated elasticity values. These values have a low SD, and the conversion to kilopascals is similar to a direct conversion of just the mean value.

	Speed[m/s]		Elasticity[kPa]		
	Average	SD	Average	SD	Depth[cm]
8	1.35	0.14	5.4	1.1	4.0
9	1.39	0.09	5.7	0.8	3.8
10	1.36	0.12	5.4	1.0	3.8
11	1.28	0.10	4.7	0.8	3.6
12	1.42	0.11	6.0	1.0	3.6

Figure 7. Shear wave elastographic report page showing 4 SWS values and the calculated elasticity values. These values have a high SD, and the conversion to kilopascals has a large discrepancy with a mathematical conversion of the mean speed value to kilopascals alone.

	Speed[m/s]		Elasticity[kPa]		
	Average	SD	Average	SD	Depth[cm]
1	1.83	1.10	15.9	12.9	5.3
2	1.36	0.94	10.3	10.2	6.2
3	1.45	0.65	8.3	6.0	5.7
4	1.27	0.48	6.0	2.8	5.8

Conclusions

The reliability of shear wave propagation can be affected by US artifacts, and the use of indicators of reliability provided by US vendors should include the inspection of the SD of the mean SWS. These factors are important to assist the operator in effective placement of the ROI and should be regarded as important considerations when using 2D SWE for the assessment of tissue stiffness.

References

1. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography, part 1: basic principles and technology. *Ultraschall Med* 2013; 34:169–184.
2. Rouze NC, Wang MH, Palmeri ML, Nightingale KR. Parameters affecting the resolution and accuracy of 2D quantitative shear wave images. *IEEE Trans Ultrason Ferroelectr Freq Control* 2012; 59:1729–1740.
3. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (long version). *Ultraschall Med* 2017; 38:e16–e47.
4. Wang M, Byram B, Palmeri M, Rouze N, Nightingale K. On the precision of time-of-flight shear wave speed estimation in homogeneous soft solids: initial results using a matrix array transducer. *IEEE Trans Ultrason Ferroelectr Freq Control* 2013; 60:758–770.
5. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography, part 1: basic principles and terminology. *Ultrasound Med Biol* 2015; 41: 1126–1147.
6. Ferraioli G, Wong VW, Castera L, et al. Liver ultrasound elastography: an update to the World Federation for Ultrasound in Medicine and Biology guidelines and recommendations. *Ultrasound Med Biol* 2018; 44:2419–2440.
7. Kenney JF, Keeping ES. *Mathematics of Statistics*. New York, NY: Van Nostrand; 1951.
8. Wikipedia. Gamma distribution. Wikipedia website. https://en.wikipedia.org/wiki/Gamma_distribution. September 12, 2018.
9. Nadebaum DP, Nicoll AJ, Sood S, Gorelik A, Gibson RN. Variability of liver shear wave measurements using a new ultrasound elastographic technique. *J Ultrasound Med* 2018; 37:647–656.

Appendix II: Statements of contribution of others

Statement of contribution of others to (Shear Wave Elastography on the Uterine Cervix: Technical Development for the Transvaginal Approach)

O'Hara S, Zelesco M, Sun Z. Shear Wave Elastography on the Uterine Cervix: Technical Development for the Transvaginal Approach. J Ultrasound Med. 2019; 38(4):1049-1060.

To whom it may concern

I, Sandra O'Hara contributed (I designed the paper, collected the data and images used and wrote the manuscript) to the paper (Shear Wave Elastography on the Uterine Cervix: Technical Development for the Transvaginal Approach)

Sandra O'Hara

I, as a Co-Author, endorse that this level of contribution by the candidate indicated above is appropriate

Marilyn Zelesco

Zhonghua Sun

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Title of your thesis / dissertation	Can shear wave elastography of the maternal cervix be of use in the prediction of Preterm Birth?
Expected completion date	Mar 2020
Expected size (number of pages)	250
Requestor Location	Curtin University Kent St Bentley, Ms. 6102 Australia Attn: Curtin University
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Shear Wave Elastography on the Uterine Cervix

Technical Development for the Transvaginal Approach

Sandra O'Hara, MMS, DMU, AMS, AFASA, Marilyn Zelesco, BSc, MSc, AMS, FIR, Zhonghua Sun, PhD, FSCCT

Objectives—This research aimed to identify biological and technical confounders in the nonpregnant cervix when applying shear wave elastography with an endovaginal transducer.

Methods—Cervical speed measurements were obtained at the internal and external os in the anterior and posterior portions of the cervix using a transvaginal approach in 69 nongravid patients.

Results—Reliable measurements were obtained at the external os and internal os, anteriorly and posteriorly, in 63, 55, 55, and 26 patients, respectively. The mean speed obtained at the external os, anteriorly and posteriorly, was 2.52 ± 0.49 m/s and 2.87 ± 0.63 m/s, respectively, and at the internal os, anteriorly and posteriorly, 3.29 ± 0.79 m/s and 4.10 ± 1.11 m/s, respectively. The difference in speed between all regions was statistically significant ($P < .05$).

Conclusion—Ultrasound-induced artifacts appear to affect the transmission of the elastographic main pulse, with cervical position contributing to suboptimal shear wave production in the posterior cervix. Reliable shear wave propagation can be achieved in the anterior cervix in most patients.

Key Words—cervix; elastography; preterm birth; shear wave; transvaginal ultrasound

Received May 2, 2018, from the SKG Radiology, West Perth, Perth, Western Australia (S.O.); Department of Medical Radiation Sciences, Curtin University, Perth, Western Australia (S.O., Z.S.); Department of Medical Imaging, Fiona Stanley Hospital, Murdoch, Western Australia (M.Z.). Manuscript accepted for publication July 20, 2018.

The authors thank Alyce Mostert, Chandelle Hernaman, Karen Rocke, Pat Milne, and the SKG Radiology Clinical Standards Committee for their assistance with this project, and Mr Gil Stevenson for his assistance with statistical analysis.

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Abbreviations
ARFI, acoustic radiation force impluse; ICC, intraclass correlation coefficient; ROI, region of interest; SD, standard deviation; SPTB, spontaneous preterm birth; SWE, shear wave elastography; SWS, shear wave speed; TVU, transvaginal ultrasosonography

doi:10.1002/jum.14793

Retention of a pregnancy requires the cervix to maintain strength to withstand multiple forces from the uterus, from the weight of the growing fetus and amniotic sac, and also passive pressure from the uterine wall. The cervix softens and shortens throughout pregnancy and finally dilates for the fetus to be delivered vaginally. Premature softening of the cervix is associated with early shortening of cervical length and subsequent spontaneous preterm birth (SPTB).[1] The cervix can be described as soft, firm, or medium based on a digital examination, but this method is subjective to the clinician, and creates difficulties because of the expectation that the cervix will soften initially at the proximal portion.[1]

Currently, the length of the cervix assessed with transvaginal ultrasonography (TVU) is the feature that is assessed to indicate cervical strength and premature softening.[2] A short cervix has been shown to be a significant risk factor for subsequent SPTB.[3] In women with a high risk of SPTB because of medical history, a shortened cervical length on TVU has a sensitivity of over 50% for subsequent SPTB. However, in low-risk women, the sensitivity is reduced to 37%,[4,5] and the appropriate method for screening for SPTB in these women is yet to be established. With preterm birth affecting 13 million babies every year and the implications for neonatal mortality and morbity,[6] there is a need for a noninvasive technique to assess cervical strength with greater sensitivity than length alone.

Ultrasound elastography assesses mechanical properties of tissues in the region being examined. The basis for this technique is that soft tissue deforms differently from firm tissue and the elastographic images reflect this difference.[7] Utilizing strain elastography, it has been proposed that it may be possible to identify women in the historically low risk population who are at an increased risk of SPTB because of softening of the cervical tissues, which precedes a reduction in cervical length.[8] A more successful induction of labor has also been observed in patients with a softer internal os.[9]

When applied to the cervix, elastography techniques based on strain imaging have difficulties because of the lack of surrounding reference tissue and the inability to reliably quantify, and hence reproduce, transducer pressure applied to the cervix.[10] Shear wave elastography (SWE) utilizes an acoustic radiation force impluse (ARFI) excitation to produce shear waves.[11] By quantifying parameters related to the propagation of the shear wave, such as shear wave speed, one can infer an estimate of tissue stiffness.[6] It is expected that this technique will produce a more objective and reproducible mechanical evaluation of the cervix than strain elastography.[12,13]

There is promise for the use of SWE on the maternal cervix during pregnancy to assess cervical strength. It has been shown that it is feasible to examine the external os anteriorly with TVU SWE and that a reduction in speed in this region is evident in women who deliver preterm.[14] It has also been shown with SWE that the cervix softens as gestational age advances[15] and in women who have cervical ripening following induction of labor.[16] The cervix has been shown to be softer during pregnancy than in the nongravid state.[1] An increase in stiffness in the cervix has been shown in the region of cervical carcinoma with the use of strain elastography.[17] This study investigates the use of SWE with an endovaginal ultrasound technique applied to the nonpregnant human uterine cervix. Experimentation and technique development was performed on a low-risk nongravid population. The goal being to identify biological and experimental variables that affect the interpretation of shear wave speed (SWS) estimates in the nongravid population to contribute to the standardization of the technique for application in the nongravid population and in the main part to the pregnant cervix. With the consideration that there may be some differences observed in the technique applied in the obstetric popluation because of extrinsic pressure from fetal parts at the internal os.

Material and Methods

This pilot study was conducted at branches of SKG Radiology in Perth, Western Australia. A convenience sample was utilized from women presenting for a routine gynecologic ultrasound examination. All participants were between 18 and 49 years of age, menstruating regularly, with varying pregnancy history and ethnicity. All patients were required to read a patient information form and give informed consent before being enrolled in the study. Ethics approval was granted from the clinical site and the Curtin University Human Research Ethics Committee.

Data collection occurred over a 13-month period commencing in July 2016. Estimation of sample size was performed with consultation from a statistician. The research by Carlson et al[16] identified a statistically significant difference between the stiffness of cervical tissue in ripened and unripened hysterectomy specimens of the cervix utilizing SWE. The difference between the mean values and the standard deviations of the values were utilized to formulate a sample size using the equation for sample sizes for comparative research studies by Eng.[18] A level of significance of P less than .05 was utilized. This calculation resulted in a minimum of 50 normal (stiff/nonpregnant) cervices needed to formulate a baseline cervical stiffness for nonpregnant patients.

Imaging Protocol

All imaging was performed on the Canon (formerly Toshiba) Aplio 500 versions 6 and 6.5 ultrasound machines (Otawara-shi, Tochigi, Japan). Cervical stiffness measurements were acquired using the 11C3

PVT-781VTE intracavity transducer. The machine setting of a shear wave frequency of 4 MHz, tracking of 0 was employed. This setting utilizes a 4-MHz push pulse and 4-MHz tracking pulse. Shear wave speed measurements were obtained using continuous mode and the lowest frame rate setting of 1, equating to 0.4 frames per second. The elastogram map was stable for at least 3 seconds before speed measurements were obtained.[19]

Measurements were registered in the midsagittal plane of the uterine cervix, midway between the canal and serosa at the internal and external os, anterior and posterior. This plane was used as it allows operators to identify the required anatomic landmarks. Once in contact with the cervix, the transducer was withdrawn to minimize transducer pressure on the cervix while not compromising the B-mode image.

Interoperator testing was performed on 15 participants. The primary SWE operator had over 20 years of experience in the field of sonography with 2 secondary operators having less than and more than 5 years of experience, respectively. Both secondary operators underwent training in the technique before commencement of data collection. The primary and senior secondary operators are skilled in liver SWE, and all operators have experience in gynecologic and obstetric applications of ultrasonography.

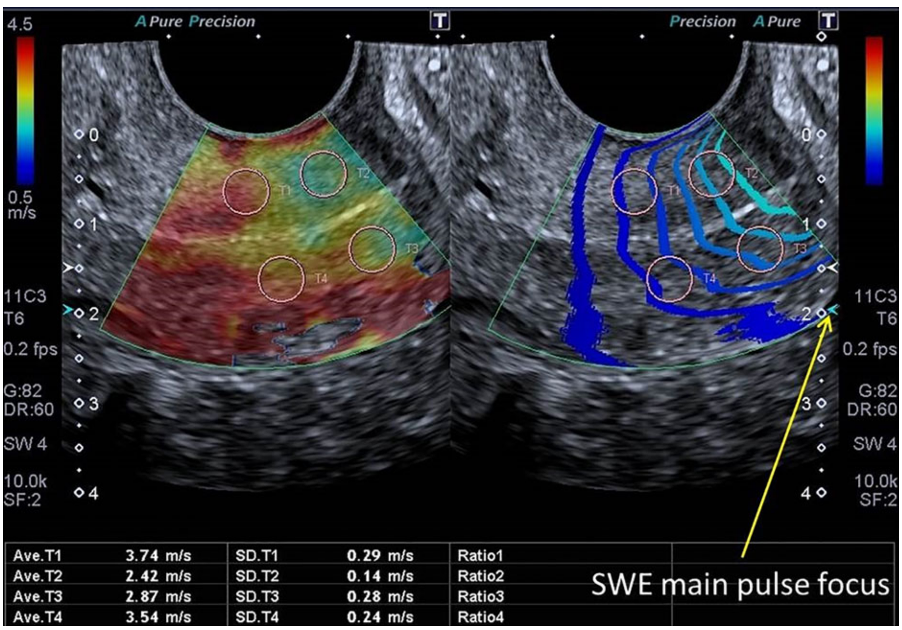
Imaging Methodology

Elastogram Map Placement

The elastogram map opacity was set to 0.3 to allow for visualization of the cervical anatomy through the elastogram. Similar to other authors,[10,15] initially (the first 8 participants) the elastogram map was placed over the entire length of both anterior and posterior portions of the cervix, with placement of all 4 regions of interest simultaneously to obtain speed measurements (Figure 1). Utilizing a large elastogram box resulted in difficulties in focusing the region of greatest sensitivity of the main pulse to the region of interest (ROI). The recent European Federation for Ultrasound in Medicine and Biology update on the use of liver ultrasound elastography recommends that the main pulse focus should be placed at the level of the ROI.[20]

To improve shear wave propagation and repeatability, the authors reduced the elastogram box size to an anterior-posterior dimension of 15 mm and the

Figure 1. Large elastogram displaying placement of 4 regions of interest in the different regions of the cervix being interrogated and the arrow highlighting the region of greatest sensitivity of the shear wave elastography main pulse.



bottom width of the box was set to 20 mm. The focus was set to the center of the elastogram box at the level of intended ROI placement. Each part of the cervix was interrogated separately so that the region of greatest sensitivity could be positioned more effectively to the anterior and posterior uterine cervix for both internal and external os (Figure 2).

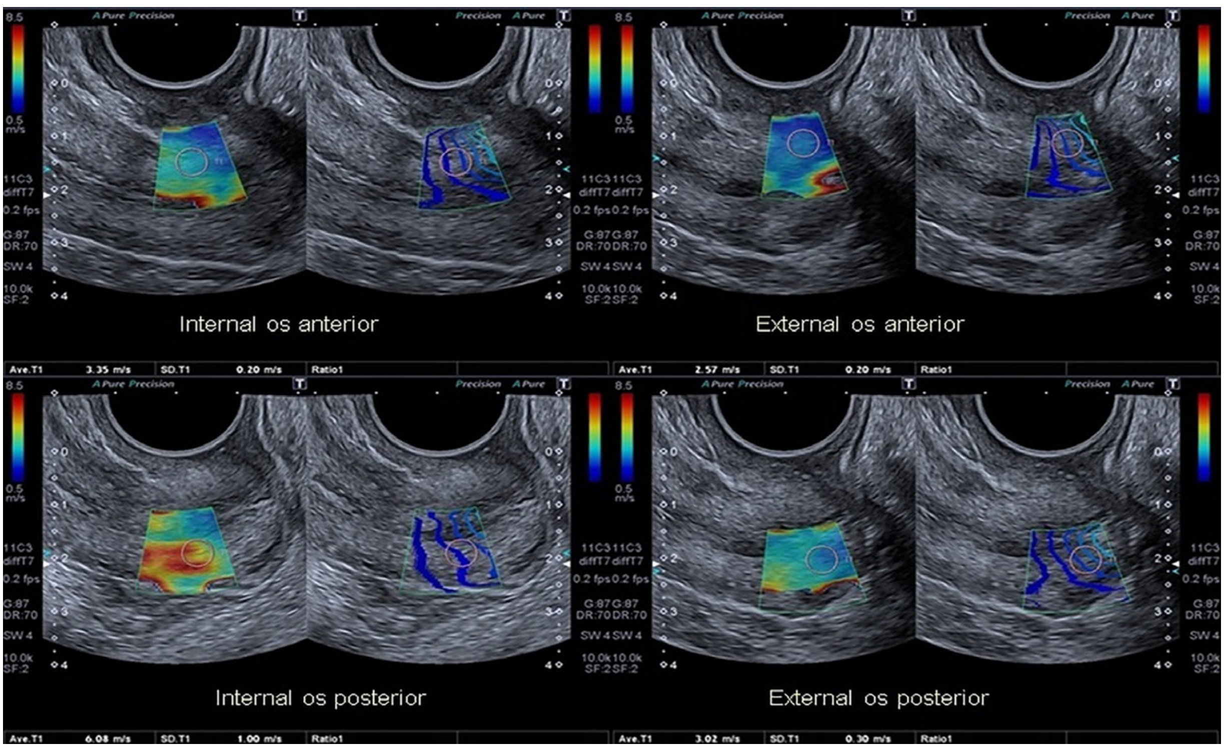
Shear Wave Region of Interest Placement

In the nongravid state the uterine cervix measures approximately 25 mm in length and 20 to 25 mm in total width, equating to an approximately 10mm width of collagenous and smooth muscle tissue around the central canal.[21] Histologic evidence shows that the cervical canal is surrounded by a layer of longitudinal smooth muscle fibers adjacent to the canal. Wrapping circumferentially around the longitudinal layer is a layer of smooth muscle and collagenous cells (Figure 3). At the internal os, there is a 50 to 60% concentration of smooth muscle cells in the circumferential layer, reducing to 40% at the midcervix, and to 10% at the external os,[22] with no appreciable difference in this structure between nulliparous and multiparous specimens.[22] The longitudinal fibers are thought to be responsible for the action of cervical effacement and the circumferential layer to prevent cervical dilatation.[21] It has been hypothesized that the circumferential layer may be acting as a "sphincter" to retain pregnancy.[21,22] A 5-mm ROI (Figure 2) has been utilized for this study to facilitate ROI placement in the circumferential layer of collagen and smooth muscles thought responsible for pregnancy retention.

Shear Wave Precision

Utilizing Canon technology, the precision of the shear wave propagation can be assessed in a number of ways. This elastogram speed map was set to a scale of 0.5 to 8.5 cm/s, with blue being indicative of softer tissues. Regions of heterogeneous color or loss of

Figure 2. Cervical shear wave elastography with reduced elastogram size and a 5-mm region of interest, showing separate interrogations at each region of the cervix, with mean speeds for the internal os anterior and posterior of 3.35 m/s and 6.08 m/s, and for the external os anterior and posterior of 2.57 m/s and 3.02 m/s, respectively.



color indicate a loss of precise shear wave propagation. A red band of color in the near field and extending into the elastogram map is indicative of increased transducer pressure on the skin or organ and vertical artifacts through the elastogram are indicative of transducer movement. As with B-mode ultrasound imaging, shear waves are also prone to scattering, reflection, or refraction, and these artifacts further affect the precision of SWS.[23] Planar wave propagation is an assumption in the estimation of SWS. The validity for this assumption can be tested using the wave front propagation maps provided by the scanner. The wave front propagation map is unique to Canon technology and indicates shear wave arrival time, as represented by contour lines. The shear wave arrival time is inversely related to the material stiffness, and thus wider spacing indicates a faster shear wave and therefore a stiffer material. The wave front map also indicates precision of shear wave propagation. Regions of highest precision are those where the contour lines are shown to be parallel and equidistant, with a loss of parallel lines being indicative of nonplanar shear wave propagation. Because of the curvature of the intracavity transducer face, there is some divergence of these parallel lines. This effect would be more apparent in the far field of the elastogram box.

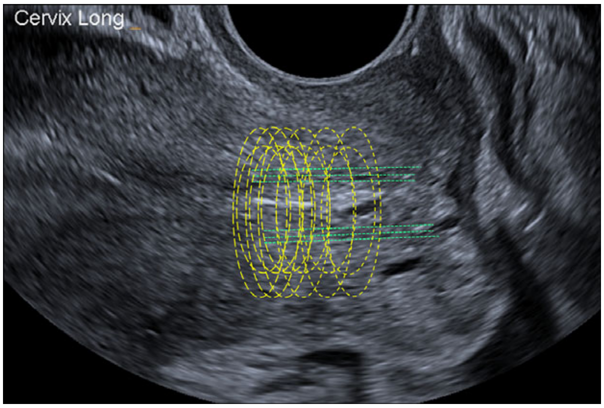


Figure 3. Ultrasound image of the uterine cervix demonstrating the central layer of smooth muscle fibers running parallel to the cervical canal and the circumferential layer of smooth muscle and collagenous fibers where the region of interest is placed for shear wave elastography sampling.

The ROI also gives indications of the precision of the shear wave propagation. Many hundreds of values are obtained from the 5mm ROI and the mean speed and 1 standard deviation (SD) of these values is displayed. The regions within the elastogram with the most homogeneous color and straightest, most parallel and equidistant propagation lines will also correlate with the lowest SD. Regions of heterogeneous or loss of color and distortion of propagation

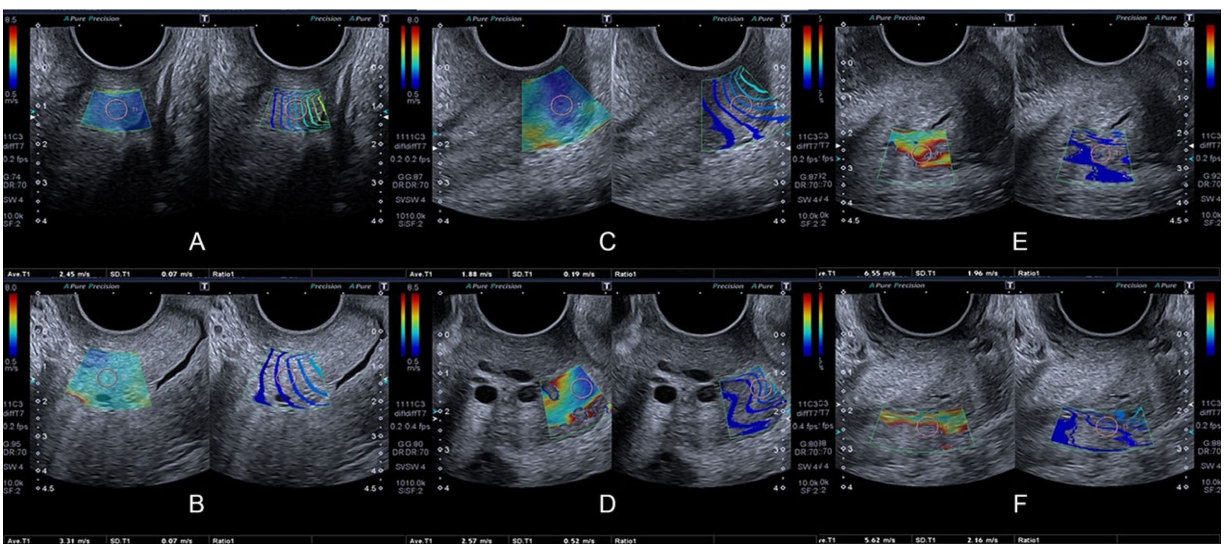


Figure 4. Example of changes in distortion of propagation lines and loss of elastogram color with increasing % of standard deviation of the mean speed: **A**, Mean speed 2.45 m/s (SD, 0.07): 2.8%; **B**, Mean speed 3.31 m/s (SD, 0.07): 2.1%; **C**, Mean speed 1.88m/s (SD, 0.19): 10%; **D**, Mean speed 2.57 m/s (SD, 0.52): 20%; **E**, Mean speed 6.55 m/s (SD, 1.96): 30%; **F**, Mean speed 5.62 m/s (SD, 2.16): 38%.

lines are indicative of nonplanar shear wave propagation; these regions also exhibit a higher SD and a higher mean speed. Figure 4 demonstrates a range of SDs obtained, ranging from an SD of 2.1% to an SD of 38% of the mean speed, with examples of the elastogram and propagation maps and mean speeds obtained.

The aforementioned factors should be considered when ascertaining the precision of the SWS. The authors considered regions of the elastogram with loss of color fill and concordant distorted propagation maps and an elevated SD to have nonplanar shear wave propagation. These qualitative factors and an SD of greater than 20% of the mean speed (quantified mathematically) was used as a cutoff above which mean SWS was considered artifactually increased and not reliable. Unreliable measurements were excluded during statistical analysis.

Transducer Pressure

As mentioned previously, the transmission of the main pulse and resultant shear waves can be affected by numerous ultrasound-induced artifacts.[23] It is ideal to optimize the B-mode image and obtain an optimal ultrasound window before the application of SWE. [20] Care should be taken to minimize probe pressure on the tissue of interest while maintaining a good B-mode window.[12] A localized prestress can result in apparent high SWS values because of nonlinear tissue responses.[23]

To assess the magnitude of this effect, we studied whether a change in transducer pressure on the cervix alters the resultant SWS. To this end, 10 participants were examined with increased and reduced transducer pressure. All regions of the cervix were interrogated as previously described. The change in distance to the ROI between increased and reduced pressure was as follows: external os anterior, 4.3 mm (2–10 mm); external os posterior, 4.2 mm (1–9 mm); internal os anterior, 4.2 mm (2–7 mm); internal os posterior, 4.2 mm (1–8 mm).

Interoperator Testing

Interoperator testing was performed on 15 participants. For each participant the first operator obtained shear wave readings at all 4 regions of interrogation. The secondary operator then performed the same set of readings at each of the 4 regions. The mean speed obtained by each operator was tested for concordance.

Statistical Analysis

Data analysis was performed using SPSS version 26.0 (IBM Corporation, Armonk, NY). Descriptive data were presented as mean ± SD. The variables were input to assess normality using a Kolmogorov-Smirnov test. The data did not differ significantly ($P > .05$) from normality. A paired samples t test was used to compare the speed measurements obtained from each region of the cervix. The null hypothesis, H_0: speed measurements from region 1 = speed measurements from region 2, which is operationalized as the paired differences in speed with a posited mean of zero, was tested against a 2-sided alternative, at the 5% level of statistical significance ($P < .05$).

Interoperator agreement compares the speed obtained from each operator using an intraclass correlation coefficient (ICC). A low level of agreement being close to 0 and a high level of agreement 1. Intraclass correlation coefficient estimates and their 95% confidence intervals (CIs) were calculated based on a mean rating ($k = 3$), absolute agreement, 2-way mixed-effects model.[24,25]

Results

Seventy-three women were considered eligible for this study. Four did not give consent to having the elastography imaging performed because of the extra time required. Sixty-nine participants had a mean age of 34 years (range, 18–49 years), with a mean gestation of 1 delivery (range, 0–8 gestations). All measurements returning an SD of greater than 20% of the mean speed were removed. Participants with 2 or more reliable measurements obtained in each region of the cervix were included in the statistical data set to facilitate a mean speed obtained over more than 1 measurement. Of the 69 participants, 3 were unsuccessful in obtaining any reliable shear wave measurements in all regions because of the cervix being in the vertical position relative to the transducer face.

The number of reliable measurements obtained in each region for the remaining 66 participants, and the mean cervical speed and SD for each region can be seen in Table 1. Stiffness results for each region were assessed for differences in concordant pairs as shown in Table 2. The number of reliable measurements obtained was assessed dependent on cervical canal position. The number of measurements obtained with differing positions of the uterine cervix are presented in Table 3, with a diagrammatic representation of the positions presented in Figure 5. Shear wave speed values for different age ranges, stage of menstrual cycle, medical history, and ethnicity are presented in Table 4. The mean speed measurements obtained with normal and reduced probe pressure are shown in Table 5.

Interoperator testing was performed on 15 participants. The external os anterior and posterior were comparable for 15 participants; the internal os anterior was comparable for 14 participants, with measurements unobtainable in 1 participant for both operators. The internal os posterior was comparable for only 6 participants, with shear wave propagation in the remaining 9 participants unobtainable for both operators. The ICC obtained at the regions of the cervix was as follows: external os anterior, 0.83 (95% CI, 0.45–0.95); external os posterior, 0.69 (95% CI, 0.07–0.90); internal os anterior, 0.92 (95% CI, 0.76–0.97), internal os posterior, 0.90 (95% CI, 0.37-0.98)

Discussion

The cervix creates a challenge in the accurate use of SWE to assess its stiffness. Spatial variations of cervical tissue composition and structure can complicate shear wave propagation. Transducer positioning is limited to the anterior fornix adjacent to the external os with transducer angulation required to interrogate the internal os. As our results show, reliable shear wave production is more likely to be produced anteriorly in the cervix, with a greater number of reliable speeds obtained at the external os than the internal

Table 1. Summary of Shear Wave Measurements Obtained for the Uterine Cervix

Participants, Total (66)	Successful Measurements Obtained (Participants)	Mean Speed (m/s)	Standard Deviation	Total Number of Successful Measurements for All Participants (of a possible 198)
External os anterior	63	2.52	0.49	184
External os posterior	55	2.87	0.63	158
Internal os anterior	55	3.29	0.79	157
Internal os posterior	26	4.10	1.11	78

Table 2. Summary of Statistical Differences in Stiffness Between Regions of the Cervix for All Participants

Comparisons	Number of Cases Compared	Mean difference in speed, m/s (SD)	Standard Error of Mean	Significance (P = .05)
External os anterior vs posterior	52	−0.44 (0.69)	0.09	$P < .001$
Internal os anterior vs posterior	22	−1.13 (1.11)	0.24	$P < .001$
Anterior internal os vs external os	55	0.79 (0.70)	0.09	$P < .001$
Posterior internal os vs external os	21	1.42 (0.88)	0.19	$P < .001$

Table 3. Summary of Number of Reliable Interrogations Registered in Each Region of the Cervix With Varying Anatomic Position

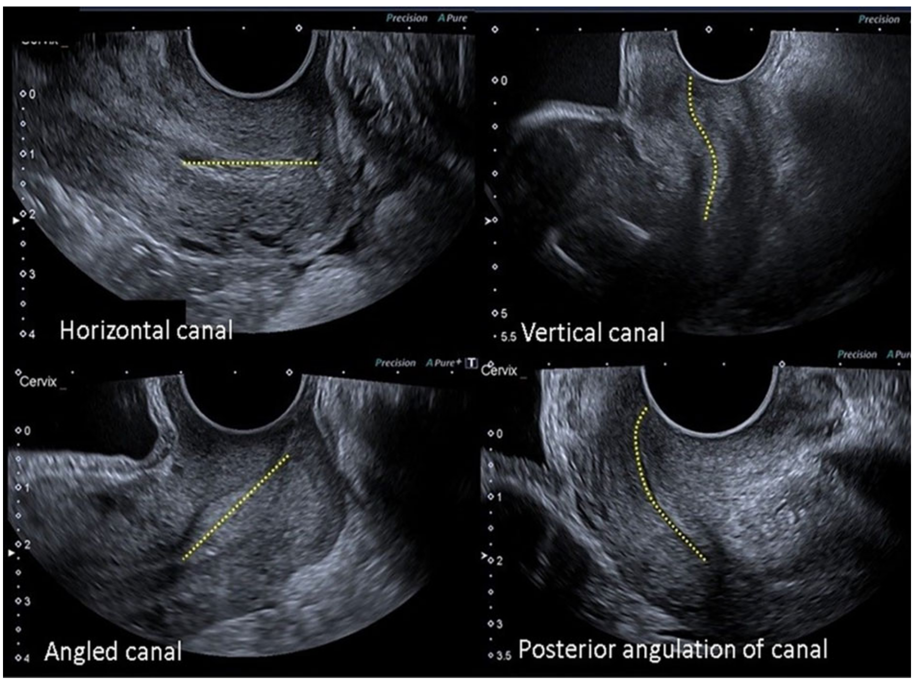
		Number of Accurate Interrogations in Each Region			
Cervical Canal Orientation	Total	External Os Anterior	External Os Posterior	Internal Os Anterior	Internal Os Posterior
Horizontal	21	21	17	20	10
Angled	33	33	30	31	11
Vertical	7	7	5	3	3
Posterior angulation	2	1	2	1	1

os. The internal os posterior is most likely to produce inaccurate or a loss of shear wave propagation in all anatomic positions, with depth of interrogation appearing to be problematic in some patients.

The research by Peralta et al[15] used SWE to measure elasticity of the external os and midcervix. This research used 6-mm ROIs at the external os, with the midcervix measurements placed at a close distance from these. In this study of 40 participants, midcervix anterior and posterior measurements were not obtainable in 1 and 2 participants, respectively.[15] Our results showed a greater proportion of unsuccessful SWE measurements at the internal os. Depending on cervical position, the posterior portion of the internal os in particular can reach a depth greater than 3 cm from the transducer face (Figure 6). A recommendation from Canon Medical (Otawara-shi, Tochigi, Japan) is that utilizing the endocavity transducer as described previously, the main push pulses can be expected to produce shear waves to a depth of 3 cm using an ultrasound phantom with an acoustic attenuation of 0.5 dB cm^{-1} MHz^{-1}. The cervix has a high acoustic attenuation of over double that of the liver, at 1.3 to 2.0 dB cm^{-1} MHz^{-1}.[6] This increased attenuation decreases the penetration depth of the main push pulse and reduces its ability to generate measurable tissue displacements.[6] The challenges for SWS estimates of the cervix with an endovaginal transducer may relate to its depth-dependent signal-to-noise ratio. In tissues, this is relative to the focal depth of the transducer, and thus the regions that are deep and proximal in the cervix can be difficult to access with the main pulse.[6]

Too much transducer pressure can produce a prestress load[23] that can falsely elevate SWSs. As shown in Table 5, increased probe pressure caused an increase in resultant SWS both anteriorly and posteriorly in the cervix. It was noted that on 2 participants the increase in pressure resulted in an improvement in shear wave propagation posterior to the cervical canal, but in most participants the prestress was transferred to both the anterior and posterior cervical

Figure 5. Example of anatomic positions of the uterine cervix that correlate to the results in Table 3. Horizontal canal: cervical canal is approximately 90° to the transducer face. Angled canal: cervical canal increases the angle with the transducer face with the external os being closer to the transducer, and internal os moving superiorly and a greater distance from the transducer face. Vertical canal: cervical canal is vertical to the transducer face. Posterior angled canal: cervical canal is at an angle to the transducer face with external os being close to the transducer and the internal os moving posteriorly and a greater distance from the transducer face.



tissues. Of note was that when the increased transducer pressure was applied, the SD of the mean speed also increased. Figure 7 is an example of the change in SWE speed obtained with gentle and then increased probe pressure. The transvaginal approach can be problematic, as a small amount of transducer pressure is required to make contact with the anterior fornix to acquire a good B-mode window prior to the application of the SWE. The transducer can be withdrawn to release this pressure, but a level of contact is still required. We conclude that precompression can alter the SWS estimation in the cervix and that nonlinear tissue responses or mechanical compression of the collagen layers by the transducer may be possible causes.

As shown in Table 4, there appears to be minimal difference in SWS between nulliparous and parous patients. There were similar speeds obtained for women with vaginal deliveries and cesarean sections and also similar speeds between ethnicities. It also appears that mostly there is an overall increase in cervical stiffness with age, and that SWE speed at the internal and external os may alter at different stages of the menstrual cycle. The cervix has been shown to alter its width and length throughout the menstrual cycle. The sphincter-like effect of the collagenous and muscular fibers at the internal os has its greatest strength during the luteal phase of ovulation and relaxes up to 2 days prior to menstruation.[21] Our results showed that the greatest speeds at the internal os were obtained during the secretory phase of the endometrium, corresponding to the luteal ovarian phase. Further research could incorporate SWS obtained during the first few days of menstruation, when the internal os should be at its softest. Larger numbers from each group would be needed to draw robust conclusions.

Table 4. Summary of Mean Speed Obtained in Each Region Dependent on Patient Characteristics

		Mean Speed in m/s and Standard Deviation for Regions of the Uterine Cervix			
Participant Characteristics	**Number of Participants**	**External Os Anterior, m/s (SD)**	**External Os Posterior, m/s (SD)**	**Internal Os Anterior, m/s (SD)**	**Internal Os Posterior, m/s (SD)**
Age range 18–25	13	2.27 (0.33)	2.61 (0.63)	3.19 (0.77)	3.67 (0.15)
Age range 26–33	16	2.47 (0.42)	2.86 (0.59)	3.02 (0.49)	4.15 (0.98)
Age range 34–41	19	2.49 (0.46)	2.96 (0.61)	3.17 (0.37)	4.10 (1.37)
Age range 42–49	18	2.77 (0.58)	2.95 (0.72)	3.66 (1.11)	4.22 (1.34)
Early Proliferative	15	2.60 (0.52)	3.04 (0.37)	3.29 (1.23)	4.87 (1.37)
Late Proliferative	24	2.39 (0.48)	2.88 (0.72)	3.22 (0.61)	4.03 (1.40)
Early Secretory	23	2.57 (0.47)	2.84 (0.66)	3.31 (0.61)	3.69 (0.49)
Late Secretory	4	2.85 (0.62)	2.46 (0.51)	4.48	4.61
Nulliparous	22	2.39 (0.47)	2.71 (0.52)	3.20 (0.59)	3.90 (0.47)
Primiparous	16	2.63 (0.41)	2.82 (0.56)	3.13 (0.58)	4.26 (0.88)
Multiparous	28	2.56 (0.53)	3.00 (0.73)	3.45 (1.01)	4.13 (1.50)
Vaginal deliveries	27	2.64 (0.477)	2.82 (0.66)	3.56 (0.95)	4.46 (1.24)
Cesarean section	13	2.45 (0.54)	3.03 (0.53)	2.89 (0.43)	3.90 (1.51)
European	46	2.54 (0.51)	2.94 (0.66)	3.41 (0.82)	4.07 (1.10)
Asian	15	2.51 (0.39)	2.74 (0.59)	3.09 (0.53)	4.47 (0.71)
Middle Eastern, Indian, and African	5	2.39 (0.50)	2.92 (0.64)	2.39 (0.87)	4.04 (1.10)

Table 5. Comparison of shear wave speeds obtained with reduced probe pressure and pressure on anterior fornix increased to a level appropriate for B-mode imaging

	External Os Anterior, m/s (SD)	**External Os Posterior, m/s (SD)**	**Internal Os Anterior, m/s (SD)**	**Internal Os Posterior, m/s (SD)**
Reduced probe pressure	2.42 (0.52)	2.64 (0.57)	3.36 (0.51)	4.62 (1.18)
Increased probe pressure	4.89 (1.79)	5.13 (1.91)	5.23 (2.04)	5.26 (0.65)

Figure 6. Shear wave elastography of the internal os posterior with a region of interest placed at a depth of 3 cm, resulting in a nonregistration of shear wave elastography measurements. The red arrow is pointing to the external os and yellow to the internal os; the endocervical mucosa and posterior margin of the cervix have been outlined in yellow and red, respectively.

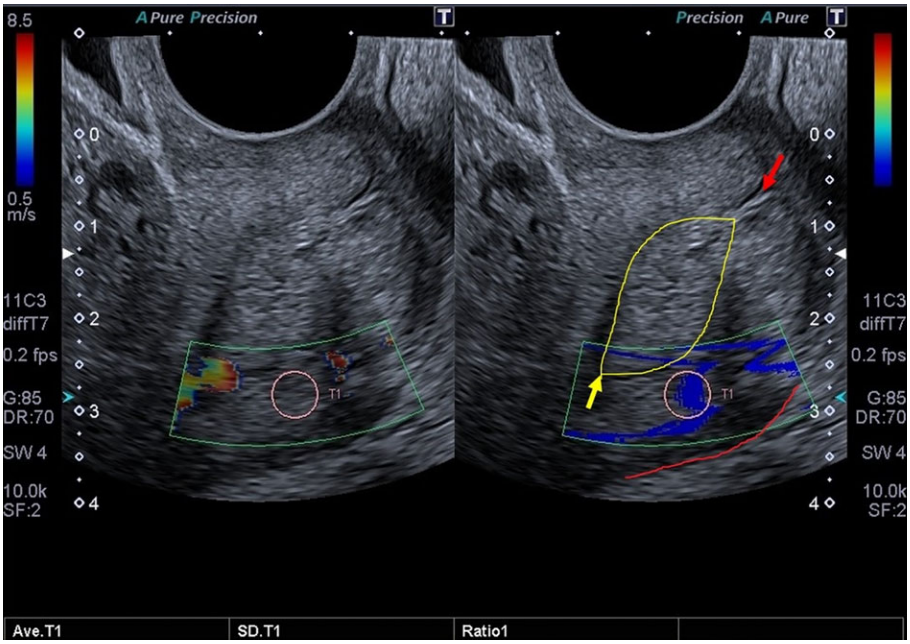
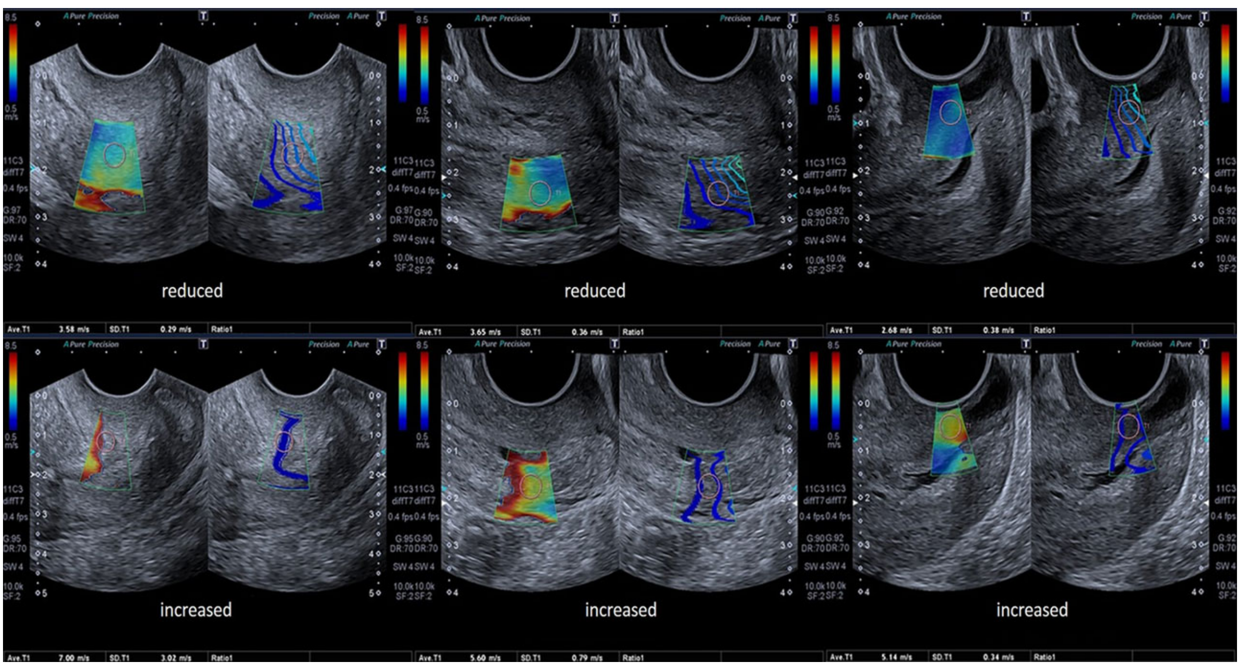


Figure 7. Shear wave elastography demonstrating changes in shear wave speeds obtained with gentle and increased probe pressure in the internal os anterior and posterior and external os anterior.



The internal os showed a significant increase in speed compared to the external os both anteriorly and posteriorly. The research by Carslon et al[26] also demonstrated this phenomenon with greater differences in SWS between the external and internal os on the unripened cervix specimens versus the specimens that had been chemically ripened.

Research into the use of strain elastography on the maternal cervix for the prediction of preterm birth documented no appreciable difference in cervical stiffness between the anterior and posterior cervix,[27] while the study by Molina et al[10] showed a reduced stiffness in strain values in the posterior cervix. As reported by Hernandez-Andrade et al[13] and Peralta et al[15] utilizing SWE, our results also show that the posterior part of the cervix appears to register a higher speed than the anterior part in this cohort, with greater differences registered at the internal than the external os. As can be seen in Figure 2, when obtainable, the arrival time of the shear wave appears to be faster in the posterior cervix, with widening of the propagation lines posteriorly compared to anteriorly. There was also a greater divergence from parallel of the propagation lines deep to the endocervical mucosa and canal in the posterior cervix, with fewer measurements being obtainable in this region. Carlson et al[26] utilized hysterectomy specimens of the cervix to obtain SWSs. The specimen was dissected, and a 9-MHz linear array transducer was used to take measurements from the canal surface of the specimen. This research found a small difference between anterior and posterior SWSs in the unripened cervix, with average speeds formulated at 3.45 ± 0.97 m/s and 3.56 ± 0.92 m/s, respectively. Larger differences were observed in ripened specimens. Our results show a larger difference in speeds obtained between the anterior and posterior cervix at the internal os, with a similar difference as Carlson et al[26] at the external os.

The cervical canal could be considered a shear wave boundary, surrounded by aligned collagen fiber bundles as previously described.[26] The appendix to the European Federation for Ultrasound in Medicine and Biology Guidelines and Recommendations[12] states that boundaries between tissues may reduce or prevent shear wave penetration across the boundary. Shear wave scattering, reflection, and refraction artifacts can also be caused by variations in tissue density, which may result in errors in shear wave estimation.[12] Material anisotropy can alter resultant SWS.[12] In patients with a cervix position ranging from angled to vertical (Figure 5), the main pulse may be approaching the collagen fibers at an angle that may cause anisotropy of the muscular collagen layer. Reducing the elastogram box size improved the interrogation of the angled cervix; however, in the vertical position the internal os is difficult to interrogate in most cases. We hypothesize that this anisotropy may be causing artifactual increases in SWS deep to the cervical canal or a loss of effective shear wave propagation.

The internal os anterior showed a good level of agreement between operators, as did the internal os posterior and external os anterior, though these regions had a broader CI reducing the reliability of the result. The external os posterior showed poor to moderate agreement with a wide confidence interval obtained for the ICC in this region.

We can conclude from this study that the attenuation properties of the cervix and shear wave artifacts are reducing the production of, and precision of, shear wave measurements deep to the cervical canal. It is important to reduce transducer pressure to the anterior fornix to minimize the prestress that may cause an increase in SWS in both the anterior and posterior cervix. The anterior cervix is more likely to produce precise shear wave values than the posterior cervix. The anatomical position of the cervix appears to affect the success of resultant shear wave measurements, the ideal being a canal that is horizontal in position.

References

1. Myers K M, Feltovich H, Mazza E, et al. The mechanical role of the cervix in pregnancy. *J Biomech* 2015; 48:1511–1523.
2. Retzke JD, Sonek JD, Lehmann J, Yazdi B, Kagan KO. Comparison of three methods of cervical measurement in the first trimester: single-line, two-line, and tracing. *Prenat Diagn* 2013; 33: 262–268.
3. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol* 2012; 206:124.e1–124.e19.
4. Larma JD, Iams JD. Is sonographic assessment of the cervix necessary and helpful? *Clin Obstet Gynecol* 2012; 55:324–335.

5. Olson Chen C. Ultrasound for cervical length. *Ultrasound Clin* 2013; 8:1–11.
6. Palmeri M, Feltovich H, Homyk A, Carlson L, Hall T. Evaluating the feasibility of acoustic radiation force impulse shear wave elasticity imaging of the uterine cervix with an intracavity array: a simulation study. *IEEE Trans Ultrason Ferroelectr Freq Control* 2013; 60: 2053–2064.
7. House M, Socrate S. The cervix as a biomechanical structure. *Ultrasound Obstet Gynecol* 2006; 28:745–749.
8. Wozniak S, Czuczwar P, Szkodziak P, et al. Elastography in predicting preterm delivery in asymptomatic, low-risk women: a prospective observational study. *BMC Pregnancy Childbirth* 2014; 14:238.
9. Preis K, Swiatkowska-Freund M, Pankrac Z. Elastography in the examination of the uterine cervix before labor induction. *Ginekol Pol* 2010; 81:757–761.
10. Molina FS, Gómez LF, Florido J, Padilla MC, Nicolaides KH. Quantification of cervical elastography: a reproducibility study. *Ultrasound Obstet Gynecol* 2012; 39:685–689.
11. Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. *J Acoust Soc Am* 2001; 110:625–634.
12. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: basic principles and technology. *Ultraschall Med* 2013; 34:169–184.
13. Hernandez-Andrade E, Hassan SS, Ahn H, et al. Evaluation of cervical stiffness during pregnancy using semiquantitative ultrasound elastography. *Ultrasound Obstet Gynecol* 2013; 41:152–161.
14. Muller M, Aït-Belkacem D, Hessabi M, et al. Assessment of the cervix in pregnant women using shear wave elastography: a feasibility study. *Ultrasound Med Biol* 2015; 41:2789–2797.
15. Peralta L, Molina FS, Melchor J, et al. Transient elastography to assess the cervical ripening during pregnancy: a preliminary study. *Ultraschall Med* 2017; 38:395–402.
16. Carlson LC, Romero ST, Palmeri ML, et al. Changes in shear wave speed pre- and post-induction of labor: a feasibility study. *Ultrasound Obstet Gynecol* 2015; 46:93–98.
17. Bakay OA, Golovko TS. Use of elastography for cervical cancer diagnostics. *Exp Oncol* 2015; 37:139–145.
18. Eng J. Sample size estimation: how many individuals should be studied? *Radiology* 2003; 227:309–313.
19. Thiele M, Detlefsen S, Sevelsted Moller L, et al. Transient and 2-dimensional shear-wave elastography provide comparable assessment of alcoholic liver fibrosis and cirrhosis. *Gastroenterology* 2016; 150:123–133.
20. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography. Update 2017 (long version). *Ultraschall Med* 2017; 38:e16–e47.
21. Nott JP, Bonney EA, Pickering JD, Simpson NAB. The structure and function of the cervix during pregnancy. *Transl Res Anatomy* 2016; 2:1–7.
22. Vink JY, Qin S, Brock CO, et al. A new paradigm for the role of smooth muscle cells in the human cervix. *Am J Obstet Gynecol* 2016; 215:478.e1.
23. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. *Ultrasound Med Biol* 2015; 41:1126–1147.
24. Fleiss JL, Cohen J. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. *Educ Psychol Measurement* 1973; 33:613–619.
25. Rankin G, Stokes M. Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. *Clin Rehabil* 1998; 12:187–199.
26. Carlson LC, Feltovich H, Palmeri ML, Rio AMd, Hall TJ. Statistical analysis of shear wave speed in the uterine cervix. *IEEE Trans Ultrason Ferroelectr Freq Control* 2014; 61:1651–1660.
27. Swiatkowska-Freund M, Preis K. Elastography of the uterine cervix: implications for success of induction of labor. *Ultrasound Obstet Gynecol* 2011; 38:52–56.

Appendix III: Statements of contribution of others

Statement of contribution of others to (Shear wave elastography of the maternal cervix: A transabdominal technique)

O'Hara S, Zelesco M, Sun Z. Shear wave elastography of the maternal cervix: A transabdominal technique. Australasian Journal of Ultrasound in Medicine. 2018; 22(2):96-103. p. 96.

To whom it may concern

I, Sandra O'Hara contributed (I designed the paper, collected the data and images used and wrote the manuscript) to the paper (Shear wave elastography of the maternal cervix: A transabdominal technique)

Sandra O'Hara

I, as a Co-Author, endorse that this level of contribution by the candidate indicated above is appropriate

Marilyn Zelesco

Zhonghua Sun

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Licensed Content Author	Zhonghua Sun, Marilyn Zelesco, Sandra O'Hara
Licensed Content Date	Nov 2, 2018
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Licensed Content Issue	2
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Title of your thesis / dissertation	Can shear wave elastography of the maternal cervix be of use in the prediction of Preterm Birth?
Expected completion date	Mar 2020
Expected size (number of pages)	250
Requestor Location	Curtin University Kent St Bentley, Ms. 6102 Australia Attn: Curtin University
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Shear wave elastography of the maternal cervix: A transabdominal technique

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Abstract

Introduction: Reduced cervical length as seen on transvaginal ultrasound is a strong indicator of spontaneous preterm birth in the high-risk population. In low-risk women the appropriate method to assess this risk is still debatable. Ultrasound elastography has been used to assess cervical strength. This research aimed to assess the accuracy of shear wave speeds (SWS) obtained deep to echo free fluid-filled structures, and the use of two-dimensional shear wave on the maternal cervix using a transabdominal ultrasound approach.

Method: Agreement of SWS measurements obtained through fluid and directly onto an ultrasound phantom was assessed for accuracy. Speed measurements were obtained in the anterior and posterior portions of the internal and external cervical os on 50 gravid participants in the mid-trimester of pregnancy.

Results: No difference in SWS was obtained in the phantom with either direct contact or through the saline water-bath ($P > 0.05$). In 50 participants, measurements were obtainable at the external os anterior and posterior in 49 and 38 participants, respectively, and in 47 and 42 participants for internal os anterior and posterior. The mean speed obtained at the external os anterior and posterior was 2.01 ± 0.51 and 2.38 ± 0.47 m/s, respectively, and at the internal os anterior and posterior, 2.49 ± 0.50 and 2.58 ± 0.41 m/s.

Conclusion: Shear wave speed measurements can be obtained in the maternal cervix using a transabdominal approach with a moderately full maternal bladder in most patients, with a larger number of shear wave measurements obtained in the anterior cervix compared to posterior.

Keywords: cervix, elastography, preterm birth, shear wave, ultrasound.

Introduction

Ultrasound shear wave elastography (SWE) is a relatively new technique that can produce a quantifiable measurement of stiffness of tissues *in vivo*. SWE utilises a modified sound wave to produce shear waves within tissues.[1] Faster shear wave speeds (SWS) are produced in stiffer tissues, with slower speeds being recorded in softer tissues.[2]

Preterm birth continues to have significant implications for the risk of neonatal mortality and morbidity,[3] with the preterm birth rate being 7.5% in Australia in 2011.[4] A shortened maternal cervix as measured by transvaginal ultrasound has been shown to be a strong indicator of subsequent spontaneous preterm birth (SPTB).[5] Even so, a shortened cervical length has a low sensitivity for SPTB in the low-risk population.[6,7] Elastographic assessment of cervical strength may have the potential to predict cervical insufficiency with greater accuracy than length alone.[2] It may be possible to identify women who are at increased risk of SPTB due to cervical softening that occurs before a reduction in cervical length with strain elastography, but this method lacks standardization between operators.[8,9] Shear wave elastography is advantageous as it provides a quantitative evaluation of the speed of propagation of the shear wave in tissues with less operator dependence.[10,11]

Research utilising an intracavity transducer and the transvaginal ultrasound approach using SWE has shown that it may be possible to identify a reduction in SWS indicating cervical softening, prior to a reduction in cervical length.[8,11] It has also been found that some patients will decline the transvaginal approach and that problems with language barriers can also

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doi: 10.1002/ajum.12116

impede consent.[12,13] The cervix has viscoelastic tissue properties that may alter during pregnancy,[14] and with preterm cervical insufficiency. This research assesses the use of a transabdominal (TA) ultrasound approach with a moderately full maternal bladder to acquire SWS in the maternal cervix.

The Canon Aplio 500 system utilises a two dimensional shear wave technology (2DSWE). 2DSWE utilises a B-mode image that is overlayed by the elastogram in real time. Ultrasound pulses are modified to a high intensity to produce shear waves in the region of interest (ROI). Shear waves cannot be produced in fluid, but it has been shown that it may be possible to obtain accurate shear wave measurements deep to echo free fluid-filled structures.[15] This research also assesses if SWS obtained with direct transducer contact onto an ultrasound phantom are the same as if the transducer is placed on a fluid-filled stand-off.

Materials and methods

Subject recruitment

This study was conducted at branches of SKG Radiology (Perth, Western Australia).

A prospective study of women presenting for their routine second trimester fetal morphology ultrasound was performed. All participants were over 18 years of age with varying pregnancy history and ethnicity, and body habitus. All participants were required to read an information sheet and give informed consent to be enrolled into the study. Exclusions were women with a multiple gestation or women already receiving vaginal progesterone or with current cervical cerclage placement. Patients unable to give informed consent due to language barriers were also excluded. Ethics approval was granted from the clinical site and Curtin University Human Research Ethics Committee.

This study represents the first 50 cases obtained as part of a larger research design and presents the use of a new technique utilising 2DSWE to obtain SWS measurements on the maternal cervix using a transabdominal approach.

Study design

All imaging was performed on the Canon Aplio 500 version 6 ultrasound machine (Otawara-shi, Tochigi, Japan), using the 6C1 curvilinear transducer. The elastogram was set to a size of 20×20 mm with the ROI set to a 5 mm sphere for the maternal cervix. The elastogram opacity was set to 0.6. Transducer shear wave frequency was 2.2 MHz with a tracking frequency of 0, equating to a 2.2 MHz push pulse and 2.2 MHz tracking pulse. A ‘continuous’ mode cine-loop of frames of >3 s of stable elastogram was stored at each region.[16] A frame rate setting of 1, equating to 0.4 frames per second was used. All data were collected by a single operator with over 20 years’ experience in the field of sonography. Intra-operator testing was performed on 20 of the participants. Shear wave speed measurements were obtained twice in each region and were compared for repeatability by the single operator.

Phantom testing

The Elastography Quality Assurance Phantom (CIRS, Norfolk, VA, USA) with a background speed of 2.94 m/s and lesion speed of 1.91 m/s was used for this experiment. This phantom was used to enable testing of the specified lesion speed with both direct transducer contact and through the saline stand-off. [Correction added on 30 November 2018, after first online publication: ‘CRIS’ has been corrected to ‘CIRS’.] The lesion is located at a depth of 3 cm, and the ROI was set to a 20 mm sphere to encompass the lesion. The transducer was supported independently with a transducer clamp and stand as shown in Figure 1. Acoustic ultrasound gel was used to facilitate transducer contact. A total of fifteen SWS measurements were acquired with the transducer in direct contact with the phantom and a further fifteen through a saline stand-off with a depth of 4.5 cm. The saline stand-off is intended to mimic the urinary bladder and to this end normal saline was utilised with an osmolality of 300 mOsm/kg,[17] similar to that of urine. Other factors remained stable as above.

Imaging methodology

The maternal bladder was partially filled to an amount required to provide a B-mode window for visualisation of the cervix posterior to the bladder, and to achieve adequate through transmission of the SWE main pulse to the cervix. The total bladder volume was variable dependant on individual participant anatomical characteristics, with bladder filling adequate to allow the superior to inferior dimension of the bladder to cover the length of the

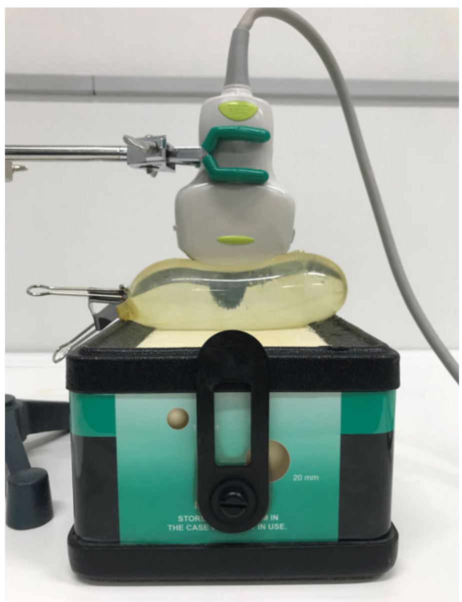

Figure 1: Image of Transducer Placement During SWS Acquisitions Using the Elastography QA Phantom with the Saline Stand-Off. Clamp and Stand Support of the Transducer is also Demonstrated.

cervical canal as demonstrated in Figures 2 and 5. The patient is placed in the supine position with transducer placement inferiorly in the midline just superior to the symphysis pubis. Measurements were acquired in the mid-sagittal plane of the cervix. The cervical canal, internal and external os were identified.[18] Transducer orientation was aligned to the length of the cervical canal and tilted to as close to a perpendicular approach to the canal as technically possible. Increasing transducer pressure has been shown to cause compression of tissues that can cause an increase in SWS, particularly in superficial tissues.[19] In this study, transducer pressure was kept to a minimum. The 5 mm ROI was positioned adjacent to the endocervical canal and mucosa and central to the outer serosal layer, in the circumferential layer of smooth muscle and collagen thought responsible for cervical dilatation.[20] Shear wave speed measurements were obtained at the internal and external os, anterior and posterior portions as can be seen in Figure 2. The mean speed was recorded three times in each anatomical location.

Shear wave speed accuracy

The main pulse used in SWE and the propagation of the shear waves can both be affected by ultrasound artifacts.[19] The Canon Aplio 500 SWE device gives indications of accuracy of shear wave propagation. The ROI registers many hundreds of SWS values simultaneously and the mean speed and one standard deviation (SD) of the values are recorded. Region of interest placement into regions of reliable shear wave propagation is aided by the use of the elastogram and propagation maps. The regions of most homogenous colour in the elastogram and the most parallel and equidistant lines on the propagation map are

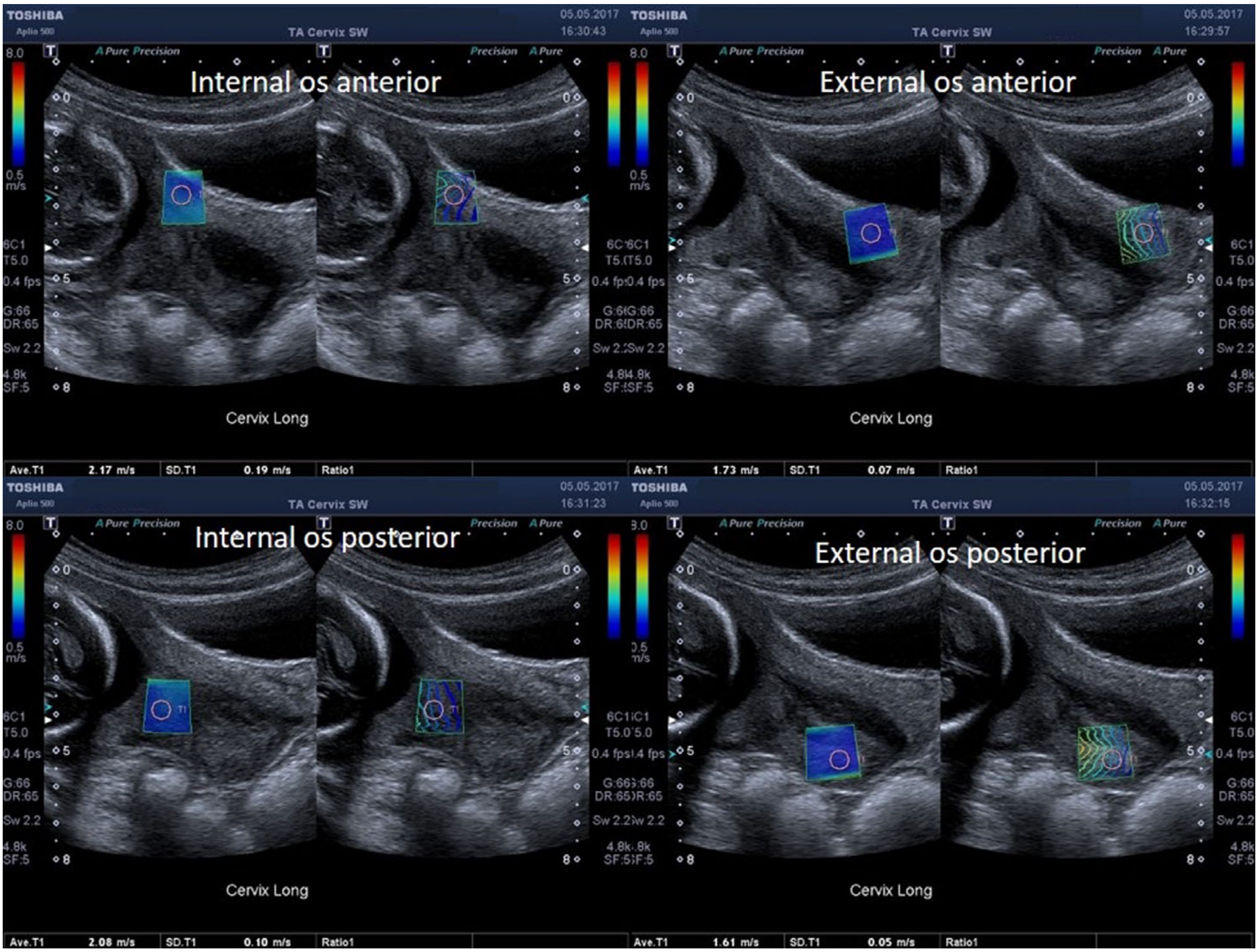

Figure 2: Example of Elastogram and ROI Placement in the Anterior and Posterior Portions of the Internal and External os. Shear Wave Speed (SWS) Obtained at the Internal os Anterior and Posteriorly is 2.17 ± 0.19 and 2.16 ± 0.12 m/s. Shear Wave Speed Obtained at the External os Anteriorly and Posteriorly were 1.73 ± 0.07 and 1.72 ± 0.06 m/s, Respectively.

indicative of consistent shear wave propagation and will return the lowest SD. Regions with in-homogenous or loss of colour fill in the elastogram and erratic lines in the propagation map are indicative of inconsistent shear wave propagation and will return a high SD. The high SD is indicative of a large variation in SWS obtained within the ROI, and measurements obtained with a high SD usually exhibit a higher mean speed than those obtained in the same region with a lower SD.

Shear wave speed measurements were obtained at the anterior and posterior portions of the internal and external os in all 50 participants. Regions exhibiting an in-homogenous or a non-filled elastogram and erratic propagation lines and an SD of >20% of the mean value were considered to be indicative of inaccurate shear wave propagation. Inaccurate measurements were excluded from the data set prior to statistical analysis. The elastogram also gives indications of increased transducer pressure, which can be identified by a red band of colour in the elastogram near field. All imaging was taken with minimal transducer pressure and devoid of the red band.

Safety considerations

It has been recommended that SWE be used with the same safety considerations as Doppler ultrasound,[19] and recommendations have been made for further investigations into the effects of SWE technology on the fetus.[21] Though Doppler technology has become standard practice for fetal examinations, for this study the elastogram was not placed on or closely adjacent to any fetal parts and use of SWE was kept to a minimum. The moderately full maternal bladder was advantageous in that the fetus was displaced cephalad from the maternal cervix.

Statistical analysis

SPSS version 26.0 (SPSS V26.0, Chicago, USA) was used to analyse data. The mean ± standard deviation (SD) was used to present continuous variables. The variables were assessed using a Kolmogorov–Smirnov Test. The data did not differ significantly ($P > 0.05$) from normality. The speed measurements acquired at each region of the cervix and for phantom testing were compared using a paired samples *t*-test. The null hypothesis used was as follows, speed measurements from region 1 = speed measurements from region 2, is formulated as the paired differences in speed with a theorised mean of zero, tested at a 5% level of statistical significance ($P < 0.05$).

Intra-operator agreement was assessed with the null hypothesis, mean bias between repeated measurements = 0 using a one-sided *t*-test. Testing incorporated a 5% level of statistical significance ($P < 0.05$).

Results

Fifty women participated in this study over a 7-month period commencing in November 2016. All participants were between 17 and 28 weeks of gestation. The mean age was 28 years (18–43 years). Varying gestational status was included with a mean gestation of 2 (0–9 gestations) and one prior delivery (1–3 deliveries). All SWS measurements obtained exhibiting a non-uniform elastogram and propagation map and an SD of >20% of the mean speed were excluded as previously described. A minimum of two reliable measurements was required to formulate the mean speed obtained at each region of the cervix. Results incorporating the number of successful measurements and mean speed for each region of the cervix are shown in Table 1, with Table 2 outlining the results of the paired *t*-test comparing the mean speed obtained at each region of the cervix.

Intra-operator testing was performed on 20 participants. Differences were not statistically different in all regions. The mean difference at external os anterior and posterior was 0.002 ± 0.03 m/s ($P = 0.789$) and 0.010 ± 0.06 m/s ($P = 0.505$), respectively. The mean difference at internal os anterior and posterior was 0.003 ± 0.04 m/s ($P = 0.735$) and -0.004 ± 0.04 m/s ($P = 0.592$) respectively.

Phantom testing

Fifteen SWS measurements were obtained in the phantom lesion with both direct transducer contact (Figure 3) and through the saline stand-off (Figure 4), with a saline depth of 4.5 cm. The mean speeds obtained in the lesion with direct contact and through the stand-off were 1.94 ± 0.04 m/s and 1.96 ± 0.01 m/s, respectively. The mean difference between SWS with saline stand-off and direct contact being -0.01 (SE 0.01); $t(15) = -1.26$ $P = 0.229$.

Discussion

Shear wave elastography utilises a sound beam modified to a high intensity, forming the main pulses that are sent vertically into the tissues to be interrogated. The main pulses create sideways movement of shear waves away from the main pulse that are tracked by the ultrasound machine in a similar way to

Table 1: Number of successful measurements and mean speeds obtained in each region of the maternal cervix.

	Successful measurements over 50 participants	Mean speed (m/s)	Standard deviation (SD)	Number of accurate measurements out of a possible 150
External os Anterior	49	2.01	±0.51	144
External os Posterior	38	2.38	±0.47	115
Internal os Anterior	47	2.49	±0.50	139
Internal os Posterior	42	2.58	±0.41	118

Table 2: Results of paired *t*-test comparing different regions of the maternal cervix.

Comparisons	Number of cases compared	Mean difference in speed (m/s) & SD	SE of mean	*t*(*df*)	Significance (P = 0.05)	Statistically significant difference
External os anterior vs. posterior	38	−0.46 (±0.45)	0.07	−6.33 (37)	.001	Yes
Internal os anterior vs. posterior	41	−0.10 (±0.56)	0.09	−1.18 (40)	.243	No
Anterior internal os vs. external os	44	0.48 (±0.39)	0.06	8.01 (43)	.001	Yes
Posterior internal os vs. external os	36	0.188 (±0.19)	0.51	2.20 (35)	.035	Yes

SD, Standard Deviation.

Doppler technology.[19] The main pulse can also be focused to the region of interrogation to improve reliability.[15] As opposed to other SWE devices, 2DSWE is able to be utilised deep to echo free fluid-filled structures.[15]

Results of the phantom testing showed that it is possible to obtain accurate SWS measurements with 2DSWE when placing the elastogram deep to an echo free fluid-filled structure. The comparison of SWS measurements obtained in the ROI with and without the fluid-filled stand-off showed no significant difference between SWS obtained.

In this study, the cervix is visualised with a moderately full maternal bladder. As with B-mode imaging, the bladder was used as an acoustic window to visualise the maternal cervix deep to this and to also allow transmission of the main pulses used in 2DSWE to the cervix. Though shear waves cannot be produced in fluid-filled structures,[10] it is possible to produce shear waves in tissues deep to the fluid-filled structure if we place the elastogram in this region as shown in Figures 1 and 5.

A recommendation for 2DSWE in the liver is that reliable shear wave propagation can be produced at a depth of up to

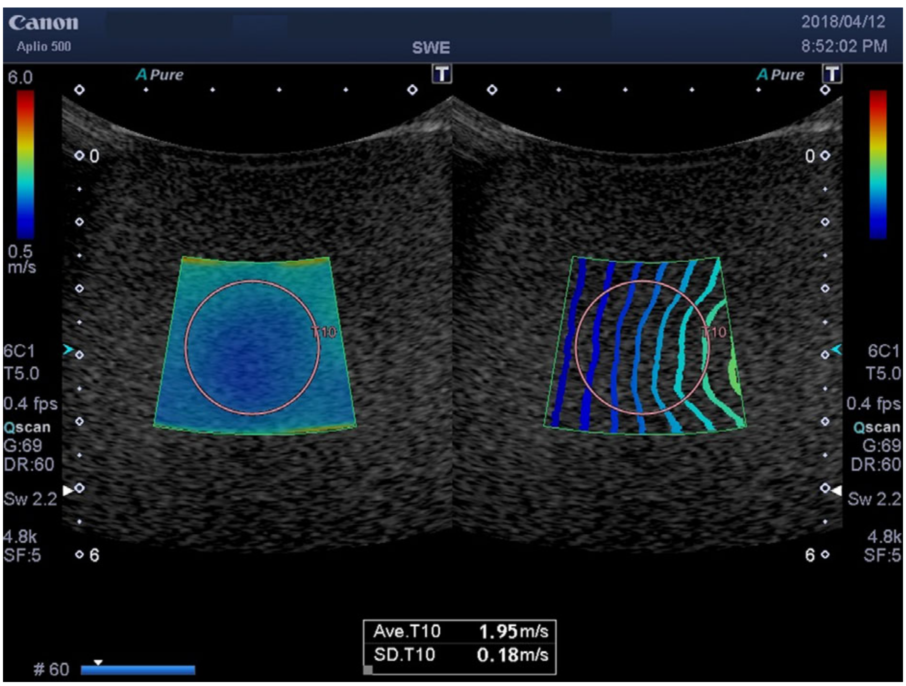

Figure 3: Shear Wave Speed Measurement Obtained at the Level of Interest in the Elastography QA Phantom with Direct Transducer Contact. Mean Speed of 1.95 ± 0.18 ms.

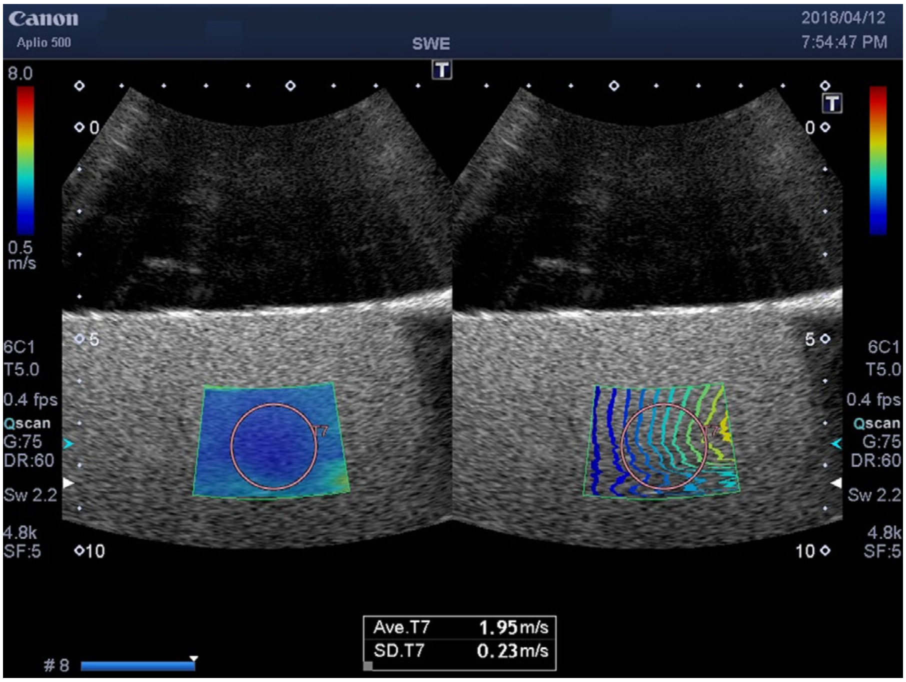

Figure 4: Shear Wave Speed Measurement Obtained at the Level of Interest in the Elastography QA Phantom with Saline Stand-Off at a Depth of 4.5 cm. Mean Speed of 1.95 ± 0.23 ms.

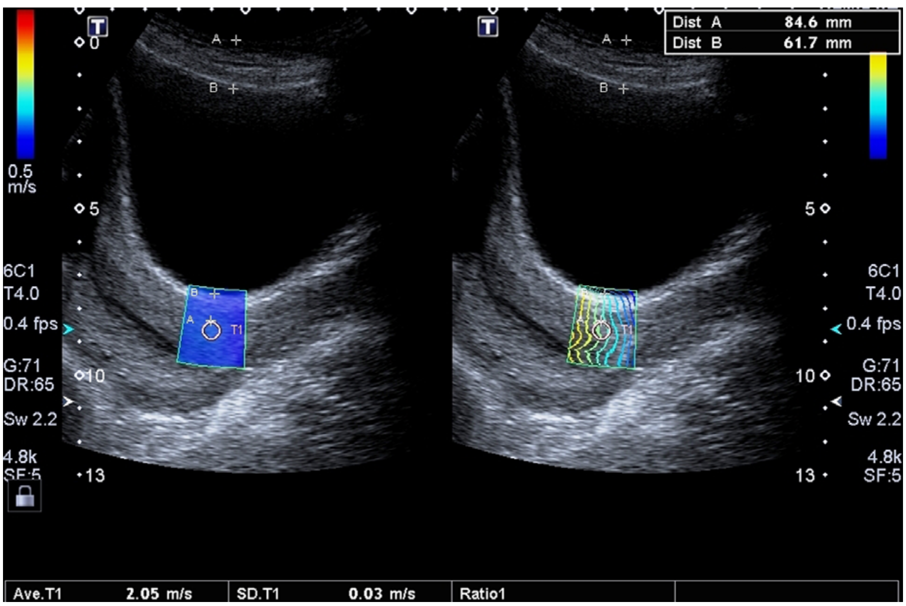

Figure 5: Region of Interest (ROI) Placed at External os Anterior with a Depth Measurement of 84.6 mm to the ROI; Bladder Height is Measured to be 61.7 mm and the Depth of Tissues Measured at 22.9 mm.

7 cm from the transducer face.[15] As Figure 5 demonstrates it appears possible to produce reliable shear wave propagation at a depth >7 cm from the transducer face to the cervix through the maternal bladder. The ROI placement in Figure 5 can be seen at a depth of 84.6 mm from the transducer face. The depth of the maternal bladder is measured at 61.7 mm and the overall depth of tissue to the ROI is measured at close to 22.9 mm.

For the 50 participants presented in this study, the greatest number of reliable SWS speed measurements were obtained at the external os anterior at 49, with 47 measurements obtained at the internal os anterior. The least number of reliable measurements were obtained at the external os posterior at 38, with the internal os posterior achieving 42 reliable SWS measurements. A greater depth of the main pulse penetration from the transducer face is required to reach the posterior cervix and produce shear wave propagation. As demonstrated in Figures 2 and 5, the external os posterior is at the greatest depth from the transducer face in most patients, and this is the region that produced the least number of reliable SWS values for this study.

It is an observation from the results of these 50 participants that a cervical canal close to horizontal in orientation so that the internal and external os is at a similar distance to the transducer face, is the most optimal position to obtain reliable shear wave propagation in all regions. When there is an anterior angulation of the internal os, the internal os is markedly closer to the transducer than the external os and the depth to the external os from the transducer face can be problematic. Increasing depth to all regions of the cervix may be a factor in patients with a large body mass index. A consideration for penetration of the main pulse to the posterior portion of the cervix is the acoustic attenuation properties of the cervix. The cervix has an acoustic attenuation of at 1.3–2.0 dB/cm/MHz, which is over twice the acoustic attenuation of the liver.[3] It would thus be an expectation that the distance of penetration of the main pulse is reduced in the cervix compared to what would be expected in the liver. The cervical canal also has opposing layers of mucosa surrounding a central canal, and it has also been shown that tissue interfaces may be problematic in shear wave elastography.[22]

The results of this study have shown a statistically significant difference between SWS obtained in the anterior compared to the posterior external os, with the posterior external os registering a higher mean speed. Interestingly, our results showed no statistical difference between the anterior and posterior internal os. Hernandez *et al.*[11] reported an increase in SWS in the cervix posteriorly using a transvaginal ultrasound approach as did Carlson *et al.*[22] using a linear array transducer to measure SWS on chemically ripened and unripened specimens of the cervix. This study reported a small difference in SWS obtained between the anterior and posterior cervix, with greater speeds obtained in the posterior portion, and these differences were greater in the ripened specimens.[22] Using a transvaginal ultrasound approach, Peralta *et al.*[23] also found increased stiffness in the posterior cervix using SWE and research into the use of strain elastography has shown no difference or reduced stiffness posteriorly in the cervix.[8,24] As reported by Carlson *et al.*[22] and Peralta *et al.*,[23] the results of this research has also shown an increase in SWS obtained at the internal os compared to the external os, both anteriorly and posteriorly.

The one experienced operator in this study showed good reproducibility of SWS in each region of the cervix, but this study is limited by the data collection being performed by one operator. A recommendation would be that this technique is now disseminated to other operators with varying levels of experience and inter-operator testing be performed to assess the reproducibility of the technique.

Conclusion

Results of this study show that it is possible to measure SWS in the maternal cervix using a transabdominal approach. A larger number of accurate shear wave measurements can be obtained in the anterior cervix compared to the posterior, with higher SWS obtained at the internal os compared to external os. Further assessment of SWS obtained in the maternal cervix may be useful for the identification of softening of the cervical tissues and their possible relationship to cervical insufficiency and SPTB. Practical application of this technology could be the use of a non-invasive technique to assess cervical strength in the mid-trimester, with the potential to predict imminent cervical insufficiency and subsequent SPTB with a greater sensitivity than cervical length alone.

Acknowledgements

The author would like to acknowledge the assistance of Karen Rocke and also Mr Gil Stevenson for his help with Statistical analysis, and Mr Koichiro Kurita for his assistance with the phantom testing.

Disclosures of conflict of interest

S.J.O. declared no relevant relationships. M.Z. declared no relevant relationships. Z.S. declared no relevant relationships.

Authorship

All authors as listed above are in agreement with the contents of the submitted article.

Financial support

Shear wave technology utilised in this research is funded by Canon Medical Systems ANZ Pty Limited.

References

1 Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. *J Acoust Soc Am* 2001; 110(1): 625–34.
2 House M, Socrate S. The cervix as a biomechanical structure. *Ultrasound Obstet Gynecol* 2006; 28(6): 745–9.
3 Palmeri M, Feltovich H, Homyk A, Carlson L, Hall T. Evaluating the feasibility of acoustic radiation force impulse shear wave elasticity imaging of the uterine cervix with an intracavity array: a simulation study. *IEEE Trans Ultrason Ferroelectr Freq Control* 2013; 60(10): 2053–64.
4 Li ZZR, Hilder L, Sullivan EA. Australia's mothers and babies 2011. Canberra: AIHW; 2013.
5 Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, *et al.* Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and

metaanalysis of individual patient data. *Am J Obstet Gynecol* 2012; 206(2): 124.e1–19.
6 Larma JD, Iams JD. Is sonographic assessment of the cervix necessary and helpful? *Clin Obstet Gynecol* 2012; 55(1): 324–35.
7 Olson Chen C. Ultrasound for cervical length. *Ultrasound Clin* 2013; 8(1): 1–11.
8 Molina FS, Gómez LF, Florido J, Padilla MC, Nicolaides KH. Quantification of cervical elastography: a reproducibility study. *Ultrasound Obstet Gynecol* 2012; 39: 685–9.
9 Wozniak S, Czuczwar P, Szkodziak P, Milart P, Wozniakowska E, Paszkowski T. Elastography in predicting preterm delivery in asymptomatic, low-risk women: a prospective observational study. *BMC Pregnancy Childbirth* 2014; 14(1): 238.
10 Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, *et al.* EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. *Ultraschall Med* 2013; 34(2): 169–84.
11 Hernandez-Andrade E, Hassan SS, Ahn H, Korzeniewski SJ, Yeo L, Chaiworapongsa T, *et al.* Evaluation of cervical stiffness during pregnancy using semiquantitative ultrasound elastography. *Ultrasound Obstet Gynecol* 2013; 41: 152–61.
12 Orzechowski KM, Boelig RC, Baxter JK, Berghella V. A universal transvaginal cervical length screening program for preterm birth prevention. *Obstet Gynecol* 2014; 124(3): 520–5.
13 Orzechowski KM, Boelig R, Nicholas SS, Baxter J, Berghella V. Is universal cervical length screening indicated in women with prior term birth? *Am J Obstet Gynecol* 2015; 212(2): 234.e1–5.
14 Callejas A, Gomez A, Melchor J, Riveiro M, Massó P, Torres J, *et al.* Performance study of a torsional wave sensor and cervical tissue characterization. *Sensors (Basel)* 2017; 17(9): E2078.
15 Dietrich CF, Bamber J, Berzigotti A, Bota S, Cantisani V, Castera L, *et al.* EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (long version). *Ultraschall Med* 2017; 38(4): e16–47.
16 Thiele M, Detlefsen S, Sevelsted Moller L, Madsen BS, Fuglsang Hansen J, Fialla AD, *et al.* Transient and 2-dimensional shear-wave elastography provide comparable assessment of alcoholic liver fibrosis and cirrhosis. *Gastroenterology* 2016; 150(1): 123–33.
17 Koeppen BM, Stanton BA. 5 - regulation of body fluid osmolality: regulation of water balance. Renal physiology, 5th edn. Philadelphia: Mosby; 2013. 73–92.
18 O'Hara S, Zelesco M, Sun Z. A comparison of ultrasonic measurement techniques for the maternal cervix in the second trimester. *Australas J Ultrasound Med* 2015; 18(3): 118–23.
19 Shiina T, Nightingale KR, Palmeri ML, Hall TJ, Bamber JC, Barr RG, *et al.* WFUMB guidelines and recommendations for clinical use of ultrasound elastography: part 1: basic principles and terminology. *Ultrasound Med Biol* 2015; 41(5): 1126–47.
20 Nott JP, Bonney EA, Pickering JD, Simpson NAB. The structure and function of the cervix during pregnancy. *Transl Res Anat* 2016; 2: 1–7.
21 Massó P, Rus G, Molina FS. Safety of elastography in fetal medicine: preliminary study on hypoacusis. *Ultrasound Obstet Gynecol* 2017; 50(5): 660–1.
22 Carlson LC, Feltovich H, Palmeri ML, Rio AM, Hall TJ. Statistical analysis of shear wave speed in the uterine cervix. *IEEE Trans Ultrason Ferroelectr Freq Control* 2014; 61(10): 1651–60.
23 Peralta L, Molina FS, Melchor J, Gómez LF, Massó P, Florido J, *et al.* Transient elastography to assess the cervical ripening during pregnancy: a preliminary study. *Ultraschall Med* 2017; 38(04): 395–402.
24 Swiatkowska-Freund M, Preis K. Elastography of the uterine cervix: implications for success of induction of labor. *Ultrasound Obstet Gynecol* 2011; 38: 52–6.

Appendix IV: Statements of contribution of others

Statement of contribution of others to (Shear wave elastography on the maternal cervix: A comparison of transvaginal and transabdominal ultrasound approaches)

O'Hara S, Zelesco M, Sun Z. Shear wave elastography on the maternal cervix: A comparison of transvaginal and transabdominal ultrasound approaches. J Ultrasound Med.2020 (under review)

To whom it may concern

I, Sandra O'Hara contributed (I designed the paper, collected the data and images used and wrote the manuscript) to the paper (Shear wave elastography on the maternal cervix: A comparison of transvaginal and transabdominal ultrasound approaches)

Sandra O'Hara

I, as a Co-Author, endorse that this level of contribution by the candidate indicated above is appropriate

Marilyn Zelesco

Zhonghua Sun

Appendix V: Statements of contribution of others

Statement of contribution of others to (Assessment of Shear wave elastography of the maternal cervix using a transabdominal ultrasound approach for the prediction of preterm birth)

O'Hara S, Zelesco M, Sun Z. Assessment of Shear wave elastography of the maternal cervix using a transabdominal ultrasound approach for the prediction of preterm birth (under preparation for submission to the Australasian Journal of Ultrasound in Medicine)

To whom it may concern

I, Sandra O'Hara contributed (I designed the paper, collected the data and images used and wrote the manuscript) to the paper (Shear wave elastography on the maternal cervix: A comparison of transvaginal and transabdominal ultrasound approaches)

Sandra O'Hara

I, as a Co-Author, endorse that this level of contribution by the candidate indicated above is appropriate

Marilyn Zelesco

Zhonghua Sun

To Whom it May Concern

I, Sandra Joyce O'Hara contributed (I designed the study, performed data collection, collated data for statistical analysis and wrote the manuscript) to the paper (Can Shear Wave Elastography be of Value in the Assessment of Cervical Strength for the Prediction of Preterm Birth?).

April 2020

I as a Co-Author, endorse that this level of contribution by the candidate indicated above is appropriate.

Zhonghua Sun
(Co-Author 1)

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