

Developments in the clinical use of ultrasonography elastography for uterine imaging

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Abstract

Early detection of changes in tissue stiffness produced by pathogenic or physiological factors in tissue structure precedes the onset of clinical symptoms. Tissue elasticity abnormalities can be an indication of pathological processes including uterine fibrosis, adenomyosis, endometrial lesions, infertility, and premature birth. Sonography, optical coherence tomography, magnetic resonance imaging, and elastography techniques based on ultra for non-invasive medical imaging are commonly used in medical settings. measurement of a patient's mechanical properties, providing information and a helpful tool for diagnosis and treatment. Ultrasound elastography (USE) is crucial to clinical practice in obstetrics and gynaecology due to its user-friendliness. Non-intrusivity and reproducibility. This article investigates USE's recent developments in intrauterine insemination, preterm birth prediction, and uterine malignancy detection, namely early diagnosis, and treatment effect evaluation.

Keywords: Elastography, ultrasonography, uterus, shear wave elastography, stiffness

Introduction

The female reproductive system is a multi-organ, complicated system with various working mechanisms that are highly regulated ^[1]. Consequently, uterine stiffness is one of the crucial mechanical factors and physical attributes of uterine tissue and is intimately associated with the uterus's biological traits ^[2].

The degree of rigidity varies among the proliferative, secretory, gestational, and non-pregnant uterine tissue cycles ^[3]. In Furthermore, certain pathogenic processes can appear as alterations in the uterine tissue's elasticity ^[4]. For the test in contrast to a healthy myometrium, uterine fibroids are defined by a change in mechanical equilibrium and more rigidity because of too much extracellular matrix ^[5]. Adenomyosis is usually diagnosed as myometrial glandular and interstitial heterotopia. Histopathology shows hyperplasia and hypertrophy of surrounding smooth muscle cells with hyper-fascicular trabecular pattern and increased extensive fibrosis and micro-vascularization ^[6,7]. Benign lesions with a tiny quantity of fibrous interstitial components, such as endometrial soft tissue and endometrial gland hyperplasia, are the source of endometrial hyperplasia, polyps, and endometrial atrophy possess a gentle rigidity and are complemented by an elevated the percentage of nucleosomes. Thus, elevated stiffness may be linked to malignant transformation ^[8]. Because of this, researching the stiffness of tumor tissue provides a thorough understanding of its traits and behaviour (Figure 1a).

Additionally, uterine tissue undergoes biomechanical adaptations because of these physiological changes. Modifications to the uterine its am collagen composition

and structure pregnancy-related injuries result in uterine tissue physiology tissue flexibility and calcium remodelling. Collagen as the cervix's elastic Fiber structure experiences quick and significant adjustments to meet its various physiological needs roles for compliance and competency in pregnancy when giving birth Additionally, elastography varies because to difficulties during pregnancy or unusual birth caused problems associated with cervical softening (Figure 1b) ^[8,9]. Therefore, evaluating cervical flexibility to forecast the results of premature delivery and labor induction may have an impact on the selection of medical intervention.

During the menstrual cycle, the endometrium passes through a receptive phase where blastocysts can invade. This time frame is known as the "window of implantation" and it has a finite length. The effectiveness of assisted reproductive technology can be considerably increased by precisely determining the window of implantation (ART) ^[10,11].

Simultaneously, transvaginal ultrasonography is commonly employed and provides a favourable chance for prompt and precise evaluation of the endometrium. Nevertheless, the clinical significance of ultra-Sonographic indicators is still unclear, and more

Research is required to draw conclusions ^[12].

Additionally, ultrasound elastography is frequently utilized to diagnose disorders of the liver, breast, thyroid, and blood arteries, among other organs. This intriguing method has been crucial to the fields of obstetrics and gynaecology. because of its reproducibility, non-invasiveness, and simplicity ^[13].

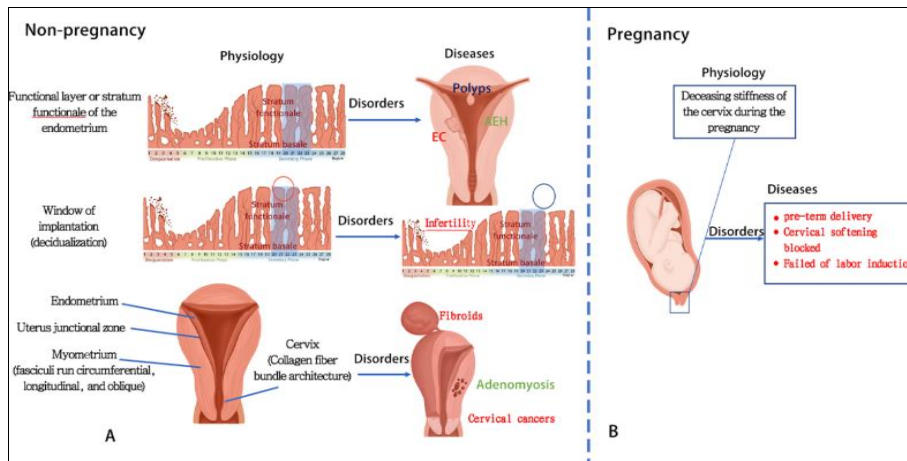


Fig 1: Stiffness may have a role in uterine diseases. Whereas B is for the gestational phase, A is for the non-gestational period. During pregnancy, endometrial polyps decrease (blue font) while uterine fibroids, EC, cervical malignancies, infertility, and cervix abnormalities become more rigid than normal tissues (red font). Adenomyosis and AEH are still unknown (green font). EC endometrial carcinoma and AEH atypical endometrial hyperplasia.

Principles of ultrasound elastography in uterine diseases

Ultrasound is the most widely used imaging diagnostic method in obstetrics and gynecology; however, it has limitations. The absence of contrast between the aberrant and surrounding tissue is one of the primary ones. Depending on the subjectivity of the operator and hence failing to Every technique for measuring and visualizing elasticity usually involves introducing a mechanical stimulation and tracking the tissue's reaction. Another drawback of ultrasonic imaging is its inability to differentiate between tissues with similar mechanical characteristics [14].

Based on the observed amount, the many USE techniques that are now available can be divided into two categories: strain imaging and shear wave imaging (SWI). This is one way to simplify the USE workflow: The intended tissue receives mechanical stimulation first, and then the displacement or shear wave produced by the target tissue is

recorded. Finally, either analogous parameters are measured or the different signals are captured on camera and encoded. (Figure 2). Mechanical stimulation is necessary for strain and SWI, and it can be categorized as follows: (A) manual compression (by hand, with the use of circulatory pulsation, respiratory motion, or both); (B) force pulse of acoustic radiation (ARFI), and (C) external vibrating mechanically. As of right now, the clinical imaging the most common diagnostic technique is strain elastography. (SE), ARFI imaging (ARFI), and transient elastography (TE) imaging), measuring the speed of shear waves, and imaging Using force impulse excitation from sonic radiation [15, 16, 17, 18]. The "strain" or deformation that results from applying a certain amount of stress to an organizational structure should be measured by strain imaging. This category includes SE and ARFI imaging, with SE being the most utilized mode in obstetrics and gynaecology.

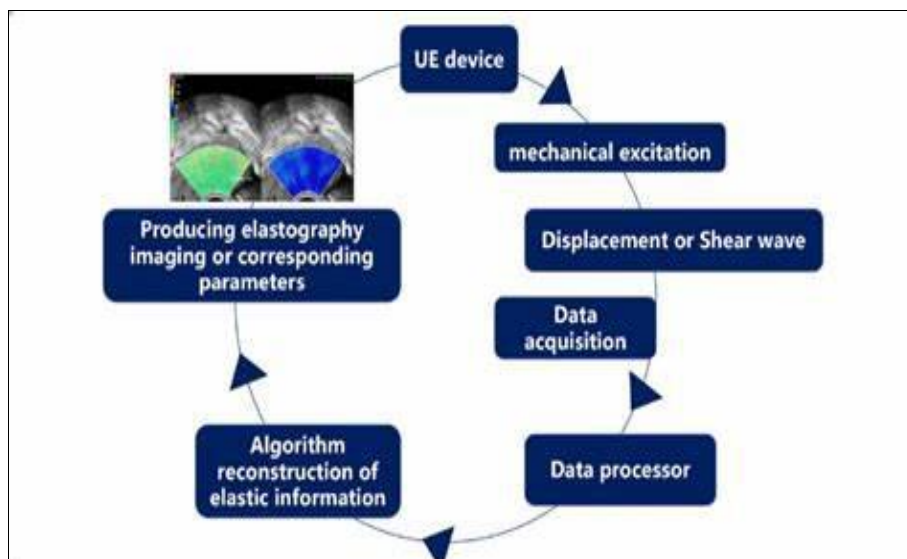


Fig 2: Flow chart of ultrasound elastography

Clinical application

Ultrasound elastography and different uterine diseases

The ability to measure tissue stiffness by ultrasonic elastography, especially shear wave elastography, has revolutionized clinical diagnosis and treatment of cervical

tumors, endometriomas, uterine fibroids, and other conditions in recent years.

Normal myometrium, uterine fibroids, and adenomyosis

The physical properties of uterine fibroids indicate that they

should have a stiffer structure than the surrounding myometrium. The present ultrasound elastography investigation of uterine fibroids (Figure 3) provides additional support for this result, with SWE providing pictures that measure uterine fibrosis [19, 20, 21]. Despite their disagreement, SE and SWE have both been demonstrated to distinguish between uterine fibroids, adenomyosis, and normal muscle layers, suggesting that SE could aid in evaluating reaction to treatment.

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Patients' quality of life is significantly impacted by adenomyosis. It is unknown, though, how adenomyosis stiffens up. The uterine junctional zone has recently the inner third of the myometrium, between the endometrium and the myometrium, is known as the JZ. There have been reports linking its structural and functional disruption to the onset and progression of adenomyosis.

In summary, USE can be used as an alternative diagnostic tool to differentiate between normal myometrium and uterine fibroids, and normal myometrium and adenomyosis, suggesting a potential role for USE in assessing treatment response.

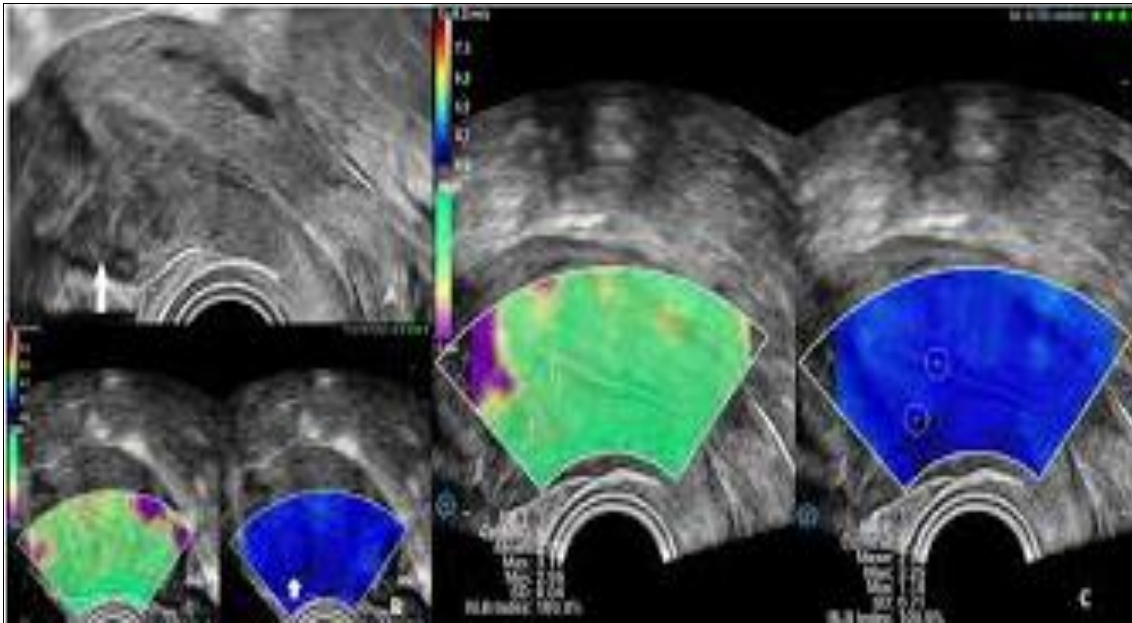


Fig 3: Uterine fibroids are diagnosed with SWE. A transvaginal ultrasound revealed a white arrow-marked hypoechoic lesion in the anterior inferior uterine region. B, SWE displayed a pseudo capsule with a lighter blue hue that circled the fibroid (shown by a white arrow). C, Finding the area of interest at lesion 2, and automatically measuring the shear wave speed (Cs).

Endometrial tumors

The USE study in endometrial tumors is still in its infancy, and the literature is limited. When B-mode sonography reveals endometrial polyps and submucosal fibroids, SE can demonstrate the varying stiffness of these lesions [22].

Cervical tumors

In gynaecology, cervical cancer (CC) is the only type of malignancy with clinical stage. FIGO states that the key to choosing treatment approaches is staging. Both SWE and SE have been utilized, to determine the extent of invasion and for the differential diagnosis of CC.

USE may have an important role in the early evaluation of chemotherapy or radiation therapy treatment efficacy in CC. Because SWE can assess the anisotropic elasticity and viscosity of cervical lesions, it is technologically superior than SE. Could facilitate the development of novel therapeutic applications and enhance diagnostic performance.

Given the viral etiology and its sexual transmission, cervical intraepithelial neoplasia (CIN) occurs mainly in young patients of reproductive age, who want to preserve their fertility.

Compared to CC, CIN has fewer pathological alterations and is a precursor to CC. USE lacks a special functionality

to identify CIN because of image noise, low resolution, and ambiguous edge recognition in images.

Infertility

The endometrium undergoes significant structural alterations during the menstrual cycle. Desquamated, the endometrium's top, functioning layer is fully shed, then rebuilt during the proliferative phase, and finally during the secretory phase.

Three-dimensional multi-frequency magnetic resonance elastography (MRE) paired with a multi-frequency dual-elastic Visco-inversion method was utilized to measure the behaviour of viscoelastic materials to vibration. MRE uses the magnitude of the complex shear modulus G , which incorporates both elastic and viscoelastic components and is determined from phase-contrast multiphase pulse sequence data, while SWI measures E or C_s . MRE is costly and time-consuming; hence, a multicentre investigation with a higher sample size using the same elastography technique and vendor is worth considering there evaluating whether SWE has substantial differences in endometrial elasticity levels in women with varied menstrual cycles.

The endometrium borders the uterine cavity, deposits the embryo, and provides the environment for the embryo to develop and grow.

SE provides a promising and innovative tool for IUI monitoring.

For abnormal elasticity, relevant procedures (another IUI with specialized treatments, in vitro fertilization, etc.) should be assessed to improve fertility outcomes.

USE does not predict the outcome of IUI when utilized independently. However, using age and ultrasonographic factors, including SE, uterine motility, uterine spiral arteries, and ultrasound elastography characteristics, can quantitatively quantify and predict pregnancy chance for clinicians. To yet, research using SWE to evaluate endometrial receptivity are sparse. Considering that SWE has the advantages of independent artificial pressure, greater objectiveness, and more repeatability, the results of using SWE instead of SE to forecast IUC demand further exploration.

Predicting pre-term delivery

Almost one-quarter of all deliveries require induction of labor (IOL), a frequent procedure in contemporary obstetrics that involves artificial labor stimulation prior to its spontaneous beginning. According to a collection of studies, SWE offers a viable way to forecast the effectiveness of IOL [23].

If one or more biomarkers are found to be predictive of PTB or IOL, therapeutic options and hospital costs may be restricted. Many techniques have been reported. In the literature to improve the use of USE in obstetrics. Although studies show that SE can greatly increase the cervix's flexibility when employing reference materials, there hasn't been any research on using this technique to cervical illnesses [23, 24].

SWE could be regarded a new non-invasive, reproducible method for monitoring fetal lung development by evaluating mechanical properties during pregnancy. In summary, we propose constructing a generalized risk prediction model including cervical elasticity, placental elasticity, and fetal LLE ratio to provide an evidence-based PTD risk assessment for clinical practice.

Prospects for the future

USE diagnosis is a promising diagnostic approach; however, its clinical use is limited due to equipment limitations and varied elastography parameters; for example, SE can only provide semiquantitative results, but SWE can provide quantitative results.

Given the advantages of SWE, the results are relatively operator-independent, while the shear wave is constant in the presence of a constant push pulse. We demonstrate that SWE is better suited for clinical application and obstetricians are educated to use a phantom setup and an operating manual is achievable.

SWE is useful for assessing how well adenomyosis and uterine fibroids respond to treatment. If USE can differentiate uterine fibroids from there is ongoing debate on adenomyosis and whether the alterations are more rigid or softer than typical myometrial tissue.

This could offer fresh perspectives and promising therapeutic target approaches for the clinical approaches used to treat adenomyosis. In addition to being helpful in determining the depth and stage of cervical cancer infiltration, USE can greatly increase the diagnostic specificity of cervical cancer. More research can concentrate on employing USE to forecast

cervical cancer chemoradiotherapy treatment response since stiffness in tumor tissues is closely correlated with tumor formation, invasion, metastasis, and resistance to chemotherapy.

Furthermore, most CIN patients who are of reproductive age and wish to have their cervix evaluated following cervical conization demonstrate the clinical significance of help maintain fertility. We assumed that examining the elastic characteristics of the cervix during cervical conization using this novel technique has a big potential to predict future pregnancies because algorithmically processed USE pictures in conjunction with HPV testing had a better diagnosis of CIN. USE can also be used to predict the outcomes of an early birth by measuring cervical softening.

Most of the research was conducted at a single location; larger investigations are required.

Evaluation of fetal lung, placental, and cervical elasticity simultaneously for final care and treatment using a precision medicine approach, SWE maturity may predict preterm birth and neonatal respiratory problems. The goal of USE's endometrial trial characteristics research will remain to determine the connection between endometrial stiffness and fertility for the foreseeable future. The therapeutic use of USE, particularly in infertility, will be further expanded with the use of SWE and the development of models to predict fertilization and pregnancy using age, uterine motility, uterine spiral arteries, and SWE features.

Conclusions

Uterine stiffness is one of the most important mechanical properties, and changes in the elasticity of uterine tissue may be a symptom of some clinical conditions.

We think that USE, especially shear wave elastography, may be a helpful method for assessing tissue stiffness, which may improve the detection of fibroids, endometrial lesions, cervical cancer, adenomyosis, and precise treatment of intrauterine growth and preterm delivery monitoring of insemination.

References

1. Elad D, Jaffa AJ, Grisaru D. Biomechanics of early life in the female reproductive tract. *Physiology*,2020;35:134–143.
2. Matsuzaki S. Mechanobiology of the female reproductive system. *Reproductive Medicine and Biology*,2021;20:371–401.
3. Sternberg AK, Buck VU, Classen-Linke I, Leube RE. How mechanical forces change the human endometrium during the menstrual cycle in preparation for embryo implantation. *Cells*,2021;10:66.
4. Peñuela LA, Fulcheri E, Vellone VG, et al. Atomic force microscopy: a promising aid in diagnosis of uterine smooth muscle neoplasms. *American Journal of Obstetrics and Gynecology*,2019;221:362–364.
5. Fang S, McLean J, Shi L, et al. Anisotropic mechanical properties of the human uterus measured by spherical indentation. *Annals of Biomedical Engineering*,2021;49:1923–1942.
6. Buggio L, Dridi D, Barbara G. Adenomyosis: impact on fertility and obstetric outcomes. *Reproductive Sciences*,2021;28:3081–3084.
7. Kirschen GW, AlAshqar A, Miyashita-Ishiwata M, et al. Vascular biology of uterine fibroids: connecting

- fibroids and vascular disorders. *Reproduction*,2021:162:R1–R18.
8. Kurek A, Kłosowicz E, Sofińska K, Jach R, Barbasz J. Methods for studying endometrial pathology and the potential of atomic force microscopy in the research of endometrium. *Cells*,2021:10:66.
 9. Sichertiu J, Meuwly JY, Baud D, Desseauve D. Using shear wave elastography to assess uterine tonicity after vaginal delivery. *Scientific Reports*,2021:11:10420.
 10. Manduca A, Bayly PJ, Ehman RL, et al. MR elastography: principles, guidelines, and terminology. *Magnetic Resonance in Medicine*,2021:85:2377–2390.
 11. Colon-Caraballo M, Lee N, Nallasamy S, et al. Novel regulatory roles of small leucine-rich proteoglycans in remodeling of the uterine cervix in pregnancy. *Matrix Biology*,2022:105:53–71.
 12. Patberg ET, Wells M, Vahanian SA, et al. Use of cervical elastography at 18 to 22 weeks' gestation in the prediction of spontaneous preterm birth. *American Journal of Obstetrics and Gynecology*,2021:225:525.e521–525.e529.
 13. Sigrist RMS, Liau J, Kaffas AE, Chammas MC, Willmann JK. Ultrasound elastography: review of techniques and clinical applications. *Theranostics*,2017:7:1303–1329.
 14. Nazzaro G, Saccone G, Miranda M, et al. Cervical elastography using E-cervix for prediction of preterm birth in singleton pregnancies with threatened preterm labor. *Journal of Maternal-Fetal and Neonatal Medicine*,2022:35:330–335.
 15. di Pasquo E, Kiener AJO, DallAsta A, et al. Evaluation of the uterine scar stiffness in women with previous Cesarean section by ultrasound elastography: a cohort study. *Clinical Imaging*,2020:64:53–56.
 16. Feltovich H, Carlson L. New techniques in evaluation of the cervix. *Seminars in Perinatology*,2017:41:477–484.
 17. 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 in Medicine and Biology*,2015:41:1126–1147.
 18. Zhang HP, Gu JY, Bai M, et al. Value of shear wave elastography with maximal elasticity in differentiating benign and malignant solid focal liver lesions. *World Journal of Gastroenterology*,2020:26:7416–7424.
 19. Jondal DE, Wang J, Chen J, et al. Uterine fibroids: correlations between MRI appearance and stiffness via magnetic resonance elastography. *Abdominal Radiology*,2018:43:1456–1463.
 20. Bildaci TB, Cevik H, Yilmaz B, Desteli GA. Value of in vitro acoustic radiation force impulse application on uterine adenomyosis. *Journal of Medical Ultrasonics*,2018:45:425–430.
 21. Stoelinga B, Hehenkamp WJK, Nieuwenhuis LL, et al. Accuracy and reproducibility of sonoelastography for the assessment of fibroids and adenomyosis, with magnetic resonance imaging as reference standard. *Ultrasound in Medicine and Biology*,2018:44:1654–1663.
 22. Gultekin IB, Imamoglu GI, Turgal M, et al. Elastasonographic evaluation of patients with a sonographic finding of thickened endometrium. *European Journal of Obstetrics Gynecology and Reproductive Biology*,2016:198:105–109.
 23. Gultekin S, Gultekin IB, Icer B, et al. Comparison of elastasonography and digital examination of cervix for consistency to predict successful vaginal delivery after induction of labor with oxytocin. *Journal of Maternal-Fetal and Neonatal Medicine*,2017:30:2795–2799.
 24. Thomsen CR, Jensen MSS, Leonhard AK, et al. A force-measuring device combined with ultrasound-based elastography for assessment of the uterine cervix. *Acta Obstetrica et Gynecologica Scandinavica*,2022:101:241–247.