Improving Detection of Intrauterine Growth Restriction via USEL by Measuring Changes to Placenta Mechanical Properties

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Introduction

- Intrauterine Growth Restriction (IUGR) occurs when the placenta cannot transfer sufficient nutrients and oxygen to the fetus baby, restricting baby's growth.
- Prevalence: 3% in developed worlds, 10-15% in developing worlds (Barut *et al*, 2010).
- Causes 5-10x higher mortality and life-long morbidities such as diabetes, heart diseases, hypertension and etc. (Saleem *et al.*, 2011).
- **Current detection rate is low** (Sherman *et al.*, 1998).
- IUGR placenta is shown to have increased apoptosis, syncytial knots (Wigglesworth, 1964) and reduced terminal villi, suggesting its mechanical properties might have altered.
- To date, no mechanical testing studies was performed on IUGR placenta.
- **Ultrasound Strain elastography (USEL), a non-invasive tool to measure tissue stiffness, can be an alternative technique to detect IUGR.**
- USEL measures the stiffness by computing the strain ratio when pressure is applied.

$$\text{Strain ratio} = \frac{\text{Fat Strain (as Reference Sample)}}{\text{Placenta Strain (as Test Sample)}}$$

- Disadvantages of USEL
  - Measurement is not comparable among patients as it uses fat layer as the reference layer. Different patients have different fat tissue stiffness.
  - Operator dependant.

Fig 1. IUGR baby (Left) vs Normal Baby (Right)

Objectives

- **Characterize mechanical properties of normal and IUGR placenta.**
- **Evaluate our proposed USEL protocols, which is :**
  - **Propose to utilize an external polymeric pad of known stiffness as reference layer and motorized movement of transducer during USEL.**

Research Methodology

IUGR Definition: Estimated fetal weight & birthweight < 10th centile

A) Mechanical Testing on Human Placenta

- 46 and 43 samples from 13 normal and 11 IUGR human placentae.
- Testing performed at x-, y-, z- directions
- Testing performed at 0.25Hz, 0.5Hz and 1.0Hz at z-direction.

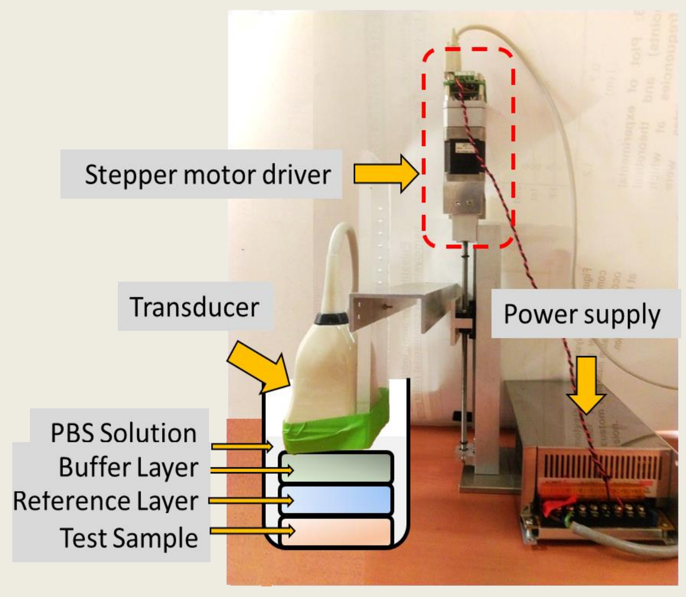


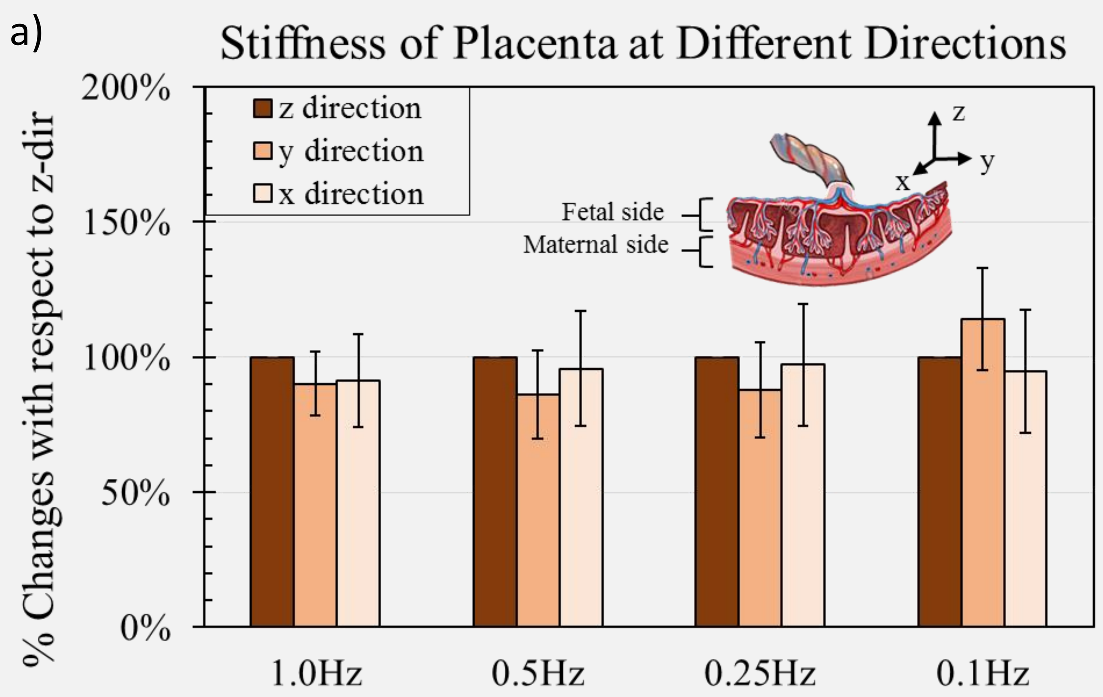
Fig 2. USEL Experiment Setup

B) Evaluation of Our Proposed USEL Protocols

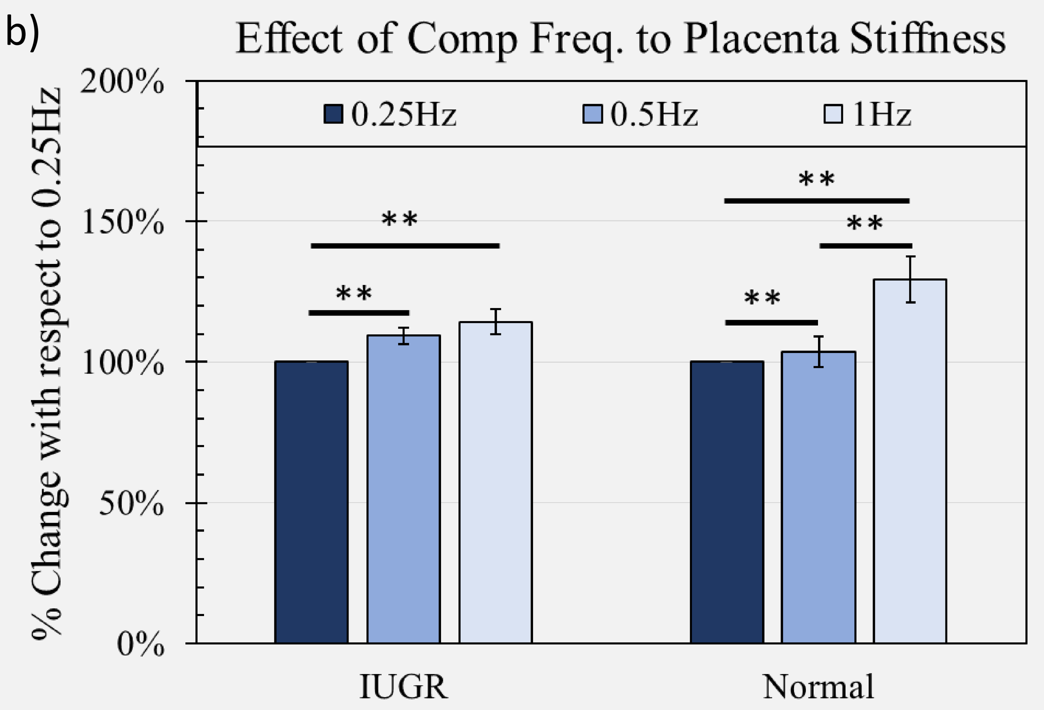
Freehand and motorized USEL
↓
Mechanical testing experiment
↓
- Validation of USEL results using mechanical testing results → Pearson Correlation btw USEL & Mechanical Testing Results
- Evaluate the precision of motorized USEL measurements → Coefficient Variation of Measurement

Results

Mechanical Properties of Human Placenta



Placenta mechanical properties were found to be isotropic.



Placenta exhibited significant viscoelastic properties, where stiffness increased at higher compression rate.

*Fig 3. (a) Placenta stiffness modulus at 20% strain tested at different directions. (b) Effect of compression frequency on placenta stiffness modulus at 20% strain tested at z-direction. **p < 0.001*

Hyperelastic Modeling

- Simple constitutive model is sufficient to describe placenta mechanical properties well.

Table 1 Goodness of fit of various constitutive models.

Constitutive Model		R^2
Fung Model $W(E) = \frac{c_0}{2}\left(e^{(c_1E_1^2+c_1E_2^2+c_1E_3^2)} - 1\right)$	Normal	0.996±0.007
	IUGR	0.996±0.005
Yeoh Model $W(I) = \sum_{i=1}^{3} C_i(I_1 - 3)^i$	Normal	0.996±0.006
	IUGR	0.996±0.004
Ogden Model $W(\lambda_1,\lambda_2,\lambda_3) = \frac{\mu}{\alpha}(\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3)$	Normal	0.995±0.010
	IUGR	0.996±0.006

Comparison between Normal and IUGR Placenta

- IUGR placenta was stiffer than normal only at low compression frequency.
- IUGR had higher collagen to elastin ratio.

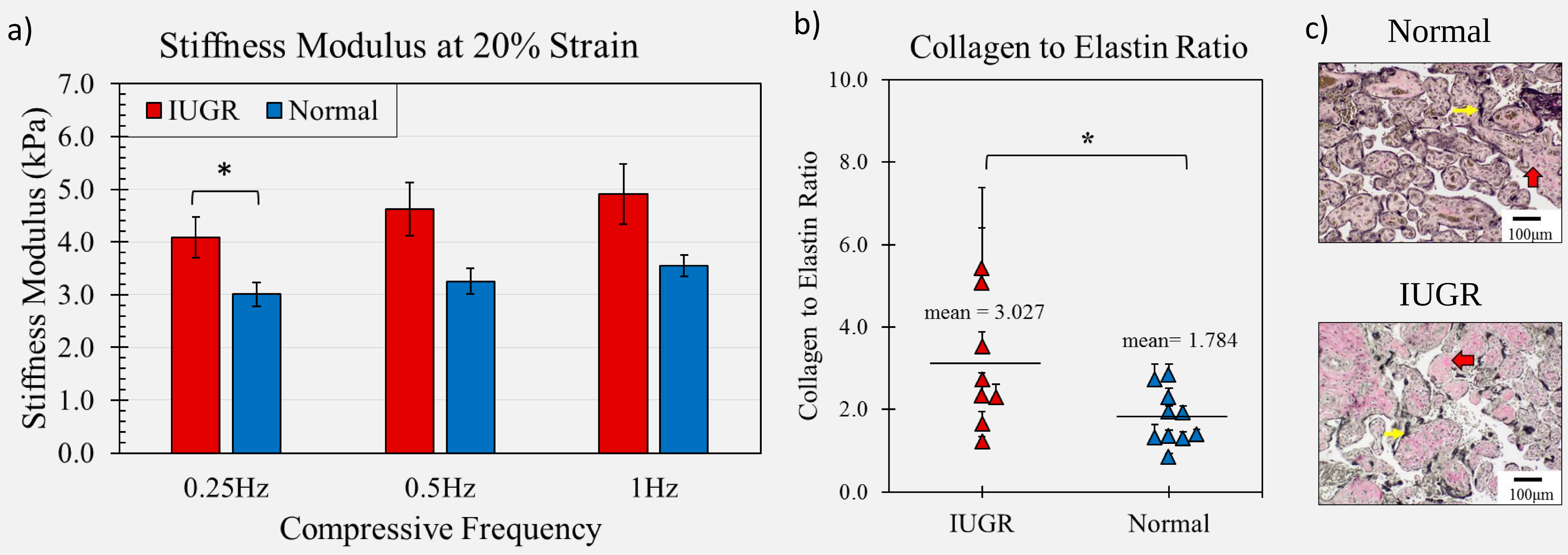


*Fig 4 (a) Placenta stiffness modulus at 20% strain. (b) Collagen to Elastin Ratio between normal and IUGR. (c) Van Verhoeff Stain of normal and IUGR placenta. Red arrow: collagen; Yellow arrow : Elastin. * p<0.05.*

Evaluation of Proposed USEL Performance on Human Placenta

- USEL yielded most accurate estimation of stiffness at low compression rate, as can be seen from the highest correlation value.
- Motorized USEL reduced measurement variability by 39%.

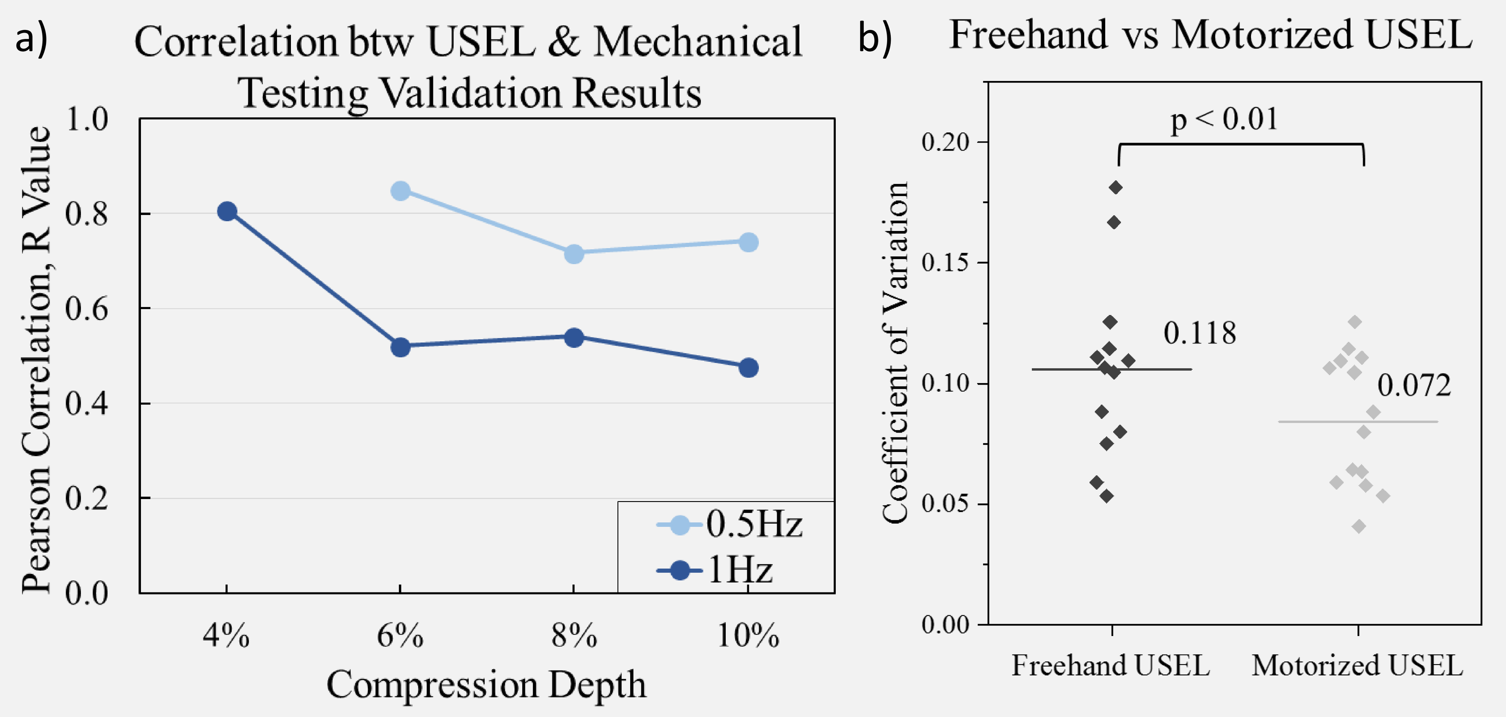


Fig 5 (a) Correlation between USEL and mechanical testing validation results. (b) Measurement variation between freehand and motorized USEL.

Conclusions

1. We had characterized the mechanical properties of human placenta.
2. Our results showed that placenta is **isotropic and viscoelastic.**
3. **IUGR placenta is stiffer** at low compression frequency only.
3. Our proposed motorized USEL protocols
   - performed better at low compression rate, 0.5Hz and
   - reduced measurement variability by 39%.

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