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Evaluation of the uterine scar stiffness in women with previous Cesarean section by ultrasound elastography: A cohort study

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Evaluation of the uterine scar stiffness in women with previous Cesarean section by ultrasound elastography: a cohort study

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Abstract:	Purpose: to evaluate by means of elastography if the quantitative assessment of the cesarean scar elasticity is feasible using as reference the surrounding intact myometrium and to investigate if the cesarean scar stiffness is influenced by the clinical characteristics of the previous cesarean delivery. Methods: prospective study including women with a previous Cesarean Section (CS) > 37 weeks' gestation performed 12-15 months before. By transvaginal ultrasound two regions of interest (ROI) were selected: uterine scar (Region 1) and surrounding myometrium (Region 2). Strain index (SI) for each ROI was calculated and the Strain Ratio (SR) was defined as Region 1 SI/Region 2 SI. The primary outcome was to compare SR among women who were grouped in accordance to presence of previous vaginal delivery (VD), CS during labor, type of suture or pyrexia during post-partum. The secondary outcome of this study was to evaluate the correlation between SR and maternal, neonatal and labor characteristics. Results: 68 women were included. The mean SR was 1.8±0.7 thus indicating an increased stiffness of the uterine scar compared to the surrounding myometrium. No significant differences were found in terms of SR according to presence of previous VD, CS during labor, type of suture or pyrexia during post-partum period. SR was not correlated to maternal characteristics nor to labor and neonatal outcome. Conclusions: evaluation of uterine scar stiffness is feasible by using elastography. The stiffness of the uterine scar is higher than that of the surrounding myometrium and is not correlated to maternal and labor characteristics
Response to Reviewers:	

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Evaluation of the uterine scar stiffness in women with previous Cesarean section by ultrasound elastography: a cohort study

Original Research

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Dear editor,

attached you will find a revised version of the manuscript entitled **"Evaluation of the uterine scar stiffness in women with previous Cesarean Section by ultrasound elastography: a cohort study"**

The paper has been modified according to the reviewer comment with changes in the text highlighted in bold. A clean version of the manuscript and an itemized response to comments are also included.

We hope that the manuscript is now suitable for the publication in your journal.

Best regards,

Tullio Ghi

Manuscript without author identifiers - with Marked/Tracked Changes

Evaluation of the uterine scar stiffness in women with previous Cesarean Section by ultrasound elastography: a cohort study

Original Research

ABSTRACT

Purpose: to evaluate by means of elastography if the quantitative assessment of the cesarean scar elasticity is feasible using as reference the surrounding intact myometrium and to investigate if the cesarean scar stiffness is influenced by the clinical characteristics of the previous cesarean delivery.

Methods: prospective study including women with a previous Cesarean Section (CS) ≥ 37 weeks' gestation performed 12-15 months before. By transvaginal ultrasound two regions of interest (ROI) were selected: uterine scar (Region 1) and surrounding myometrium (Region 2). Strain index (SI) for each ROI was calculated and the Strain Ratio (SR) was defined as Region 1 SI/Region 2 SI. The primary outcome was to compare SR among women who were grouped in accordance to presence of previous vaginal delivery, CS during labor, type of suture or pyrexia during post-partum. The secondary outcome of this study was to evaluate the correlation between SR and maternal, neonatal and labor characteristics.

Results: 68 women were included. The mean SR was 1.8±0.7 thus indicating an increased stiffness of the uterine scar compared to the surrounding myometrium. No significant differences were found in terms of SR according to presence of previous VD, CS during labor, type of suture or pyrexia during post-partum period. Strain Ratio was not correlated to maternal characteristics nor to labor and neonatal outcome.

Conclusions: evaluation of uterine scar stiffness is feasible by using elastography. The stiffness of the uterine scar is higher than that of the surrounding myometrium and is not correlated to maternal and labor characteristics

Keywords: elastography, uterine scar, Cesarean Section, ultrasound, scar stiffness

Abbreviations

CS=Cesarean Section

ROI= Region of interest

SR= Strain Ratio

SI=Strain Index

VD= Vaginal Delivery

BMI=Body Mass Index

INTRODUCTION

Since 1995 the rate of Cesarean Section (CS) has dramatically increased worldwide [1]. This trend is mainly due to the increase in frequency of primary CS but also to a decline in attempted trials of labor after CS (TOLAC) [2,3]. Although Vaginal birth after C-section (VBAC) has been shown to be a safe option for both mother and child, uterine rupture can occur in about 0.5-1.5% of women with one previous CS undergoing a TOLAC [4,5].

Many studies tried to find an effective method to predict the individual risk of uterine rupture in women with a history of CS attempting a vaginal delivery.

The vast majority of the existing literature has been focused on the correlation between the lower uterine segment (LUS) thickness measured by 2D ultrasound at 36 weeks of gestation and the risk of subsequent uterine rupture or dehiscence. However, no reliable cut off to be used in clinical practice has been found [6-9]. On the other hand, there are few studies considering the uterine scar stiffness as a possible factor influencing the risk of uterine rupture during the subsequent trial of labor [10,11]. Ultrasound elastography is a technique which provides information about the elasticity of the tissue under the mechanical stress represented by the ultrasound beam. The technique is based on the qualitative or quantitative estimation of the displacement of the target tissue when an oscillatory pressure is applied [12].

In clinical practice elastography has been used for the diagnosis and classification of liver disease, enlarged lymph nodes, breast and prostate cancer, thyroid tumors and uterine fibroids [13].

In obstetrics, the use of elastography to evaluate the cervical modifications during pregnancy and to predict the outcome of labor induction of labor has been explored by observational and reproducibility studies [14-18].

The aim of our study was to evaluate by means of elastography if the quantitative assessment of the cesarean scar elasticity is feasible using as reference the surrounding intact myometrium and to investigate if the cesarean scar stiffness is influenced by the clinical characteristics of the previous cesarean delivery.

MATERIALS AND METHODS

Study design and study population

This is a prospective cohort study conducted from February to September 2017 and including women with a previous planned or emergency CS $\geq$ 37 weeks' gestation performed 12 to 15 months before. Exclusion criteria were twin pregnancy, more than one CS, preterm CS, vertical CS, congenital uterine anomalies (ESHRE/ESGE classification of uterine anomalies: **dysmorphic infantilis uterus, complete septate uterus, bicorporeal uterus, or hemi-uterus**) [19], myomas and retroverted retroflexed uterus . Pregnant women were also excluded.

Management

Women underwent ultrasound examination using a 5.0- 7.0 MHz transvaginal probe (Esaote Mylab 60, Geneve, 5-8 MHz). Cervical measurements were performed with empty bladder and in dorsal lithotomy position placing the probe in the anterior fornix of the vagina and obtaining the visualization of the uterine scar and the sagittal view of the cervix. The uterine scar was identified as the thinnest and **hyperechoic** zone at the site of the lower uterine segment.

Two regions of interest (ROI) of about 20-23 mm^2 were selected: uterine scar (Region 1) and surrounding myometrium (Region 2) in order to evaluate tissue strain after applying a 4-5 cycles of a perpendicular oscillatory pressure through rhythmic movements on the mid-sagittal plane. The myometrial ROI was placed in the middle part of the anterior uterine wall above the region of the previous uterine scar.

Acquired data were **processed** by an appropriate software (ElaXto®; Esaote S.p.A., Genova, Italy) and shown as different color zones ranging from red, yellow, green to blue from softer to harder tissues, respectively. The software automatically displayed a strain index for each ROI. The Strain Ratio (SR), was defined as Region 1 strain index/Region 2 strain index (Figure 1).

All values >1 indicate that the numerator (Strain Index of the scarred LUS) is greater (= harder) than the denominator (Strain index of the myometrium).

Outcome

An analysis of demographics, clinical characteristics, pregnancy and delivery outcome was performed within the study group.

The primary outcome of the study was to compare Strain Ratio (SR) among women who were grouped in accordance to the following characteristics:

- Presence or absence of previous vaginal delivery (VD)
- CS during or before labor
- Single or double layer of uterine suture
- Pyrexia during the post-partum period (>38°C)

The secondary outcome of this study was to evaluate the correlation between SR and the following characteristics: maternal age, maternal Body Mass Index (BMI), number of previous VD, gestational age at delivery, neonatal weight, duration of labor and cervical dilatation at CS.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 22 (IBM Inc., Armonk, NY, USA). Data were displayed as mean±standard deviation (SD) or as number (percentage). Categorical variables were compared using the Chi-square or Fisher exact test. Between-group comparison of continuous variables was undertaken using T-test and the Mann-Whitney nonparametric equivalent test. Two-sided p-values were calculated and p values <0.05 were considered as statistically significant.

Being the SR a ratio between the Strain Index (SI) of the scarred LUS vs that of the intact myometrium, mean values ±DS >1 were assumed to indicate that the SI of the numerator was greater than that of the denominator and ultimately that the Scarred LUS was significantly stiffer than the intact myometrium. Using this approach, a significance test comparing the elasticity of the two uterine zones and yielding a p-value was not considered necessary.

Linear regression was used to assess the correlation between SR and maternal and pregnancy characteristics and correlation coefficients were expressed with corresponding significance levels. The study was performed following the STROBE guidelines [20]. This study has been approved by the local Ethics Committee.

RESULTS

Over the study period, 78 women were considered eligible for the study purpose. Of them, 5 were subsequently excluded due to the sonographic diagnosis of uterine anomalies, 4 were lost to follow up and 1 was pregnant at the time of the assessment. A total of 68 women with a mean interval-time from CS of 13.5±1.27 months **were included in the final analysis**; maternal and pregnancy characteristics are described in Table 1. The mean SR between the cesarean scar and the surrounding intact myometrium was 1.8±0.7. Overall, 59/68 (86.8%) of women had a CS during labor and 9/68(13.2%) during the second stage of labor at a mean gestational age of 39.6±1.3 weeks. The overall incidence of pyrexia during the post-partum period was 5.9% (4/68).

Table 2 describes the primary outcome of the study. No significant differences were found in terms of SR according to presence/absence of previous VD (1.56±0.45 vs 1.8±0.7; p=0.30), CS during labor (1.86±0.71 vs.1.7±0.; p=0.34), type of suture (single layer 1.7±0.6 vs double layer 1.9±0.8; p=0.13) or pyrexia during post-partum period (1.8±0.7 vs. 1.9±0.5; p=0.89). Strain Ratio was not correlated with the following maternal and labor characteristics: maternal age (p=0.36); pre-pregnant BMI (p=0.17); BMI at delivery (p=0.22), gestational age at delivery (p=0.31); number of previous VD (p=0.21); neonatal weight (p=0.91); duration of labor (0.23) and cervical dilatation at CS (p=0.45) (Table 3).

DISCUSSION

The main finding of our study is that the evaluation of uterine scar stiffness is feasible by using elastography. By means of this technique, we demonstrated that the stiffness of the uterine scar is higher than that of the surrounding myometrium and that the degree of scar stiffness is not correlated to the maternal characteristics, the intrapartum management nor the technique of uterine closure.

The hypothesis being tested is that histological changes characterizing uterine scar reparation after CS may be reflected by changes in its biomechanical properties. In particular, the higher stiffness, the reduced elasticity and tissue displacement during pressure could be determined by a lower density of smooth muscle cells and a higher collagen content [21,13].

While reproducibility studies have largely validated the use of elastography as standard technique to evaluate changes in cervical stiffness during pregnancy or induction of labor, data on the use of elastography in the assessment of LUS are lacking [14,15]. In literature there has been much interest on the sonographic antepartum assessment of the uterine scar whose features might predict the occurrence of uterine rupture or dehiscence in women with a previous Cesarean section undergoing a trial of labor.

Either the shape (scar asymmetry, wedge defects or ballooning in the LUS) and the thickness (6,9) of the scarred lower uterine segment have been sonographically investigated. A meta-analysis including 21 studies showed that there is a negative correlation between the LUS thickness and the risk of uterine rupture during subsequent trial of labor but it failed in identifying a cut-off with a good predictive value for uterine rupture mainly due to the heterogeneity of the included studies and to the lack of a standardized technique to measure LUS [6]. Some studies [22-25] have reported that the ultrasound characteristics of LUS during subsequent pregnancies may be influenced by a series of additional factors which are known to contribute to the occurrence of uterine rupture including maternal conditions, intrapartum management, techniques of uterine closure. On the other hand, recent evidences and experimental studies support the hypothesis that dehiscent or ruptured cesarean scars are characterized by an abnormal collagen content [26-28]. At the light of these observations the biomechanical properties of the lower uterine segment (LUS) in 33 women with a previous cesarean section (CS) have been assessed a few hours before repeated cesarean delivery by shear wave ultrasound (US) elastography [29]. In a few cases of this study high stiffness and restricted biomechanical resilience have been found in women with apparently normal scar and this has been proposed to explain the phenomenon of rupture during TOLAC despite a normal measurement of the LUS thickness at antepartum 2D ultrasound [26-29].

On the basis of our own data, biomechanical changes of the myometrial tissue due to the healing process at the level of the scar do not seem not to be influenced by maternal or previous pregnancy factors after an interval time of 12-15 months from CS. In this study we decided not to include pregnant women because we wanted to assess the pure effect of the previous cesarean surgery on the biomechanical properties of the lower uterine effect without the concomitant effect of other confounders such as a new pregnancy. Actually, although there is lack of data on that, we certainly envisage that the pregnant status may modify the elasticity of the uterine scar due to the related hormonal changes and to the morphological and volumetric changes of the uterus. We also decided not to include the women with retroverted/retroflexed uterus. The reason for this choice is that in this preliminary feasibility study we wanted to collect genuine and accurate data on the cesarean scar elasticity. Accordingly, we decided to exclude a priori cases of retroverted uterus because in these cases it may be difficult to insonate on the same plane and perpendicularly to the ultrasound beam the cesarean uterine scar and the surrounding intact myometrium. We cannot say that in retroverted uterus the elastography is not feasible simply because we have not tested it. However, we do not think that this is major issue as we envisage that the most promising clinical application of this technique may be the assessment of the cesarean scar elasticity in late pregnancy when the uterus is not retroverted

The prospective design, the originality in testing the sono-elastography on uterine scar and the standardization of the interval time from CS represent the main strengths of the present study. Potential confounding (ethnicity, maternal age, post-partum pyrexia) were all included in the analysis. The small sample size and the lack of evaluation of the intra and inter-observer variability are the main limitations of the study. Of course, **this study does not draw conclusions** on the correlation between biomechanical characteristics of uterine scar and subsequent risk of uterine rupture in a subsequent trial of labor due to the lack of follow-up data.

Conclusion

In conclusion, our study has shown that sonoelastography may provide reliable information about the stiffness of the cesarean uterine scar in non-pregnant women with a single previous cesarean delivery. The stiffness of the scarred LUS seems significantly increased compared with the surrounding intact myometrium but the degree of stiffness does not seem to be affected by previous obstetrical history or maternal characteristics. **It is still to demonstrate if the use of sonoelastography during pregnancy and its combination with additional sonographic findings such as the thickness of the scarred LUS could help the clinicians in identifying those women at higher risk of uterine rupture during a trial of labor after CS.**

Acknowledgments: none

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Table 1. Demographic characteristics and pregnancy outcome among 68 women with Casarean Section (CS)-uterine scar

Variables	n=68
Mean Strain Ratio (SR)	1.8±0.7
Maternal age	33.1±4.9
Caucasian	65(95.6)
Pre-pregnant BMI	23.5±3.7
BMI at delivery	28.0±3.7
Previous Vaginal Delivery	12(17.6)
Gestational Age at delivery	39.6±1.3
CS during labor	59(86.8)
CS during II stage	9(13.2)
Pyrexia during the post-partum period	4(5.9)

Data are expressed as mean±SD or n(%)

Table 2. Primary outcome

		p-value
Previous Vaginal Delivery		
Yes (n=12)	No (n=56)	0.30
1.56±0.45	1.8±0.7	
Cesarean Section during labor		
Yes (38)	No (n=30)	0.34
1.86±0.71	1.7±0.6	
Type of suture		
Single layer (n=43)	Double layer (n=25)	0.13
1.7±0.6	1.9±0.8	
Hyperpyrexia during Post-partum		
Yes (n=4)	No (n=64)	0.89
1.8±0.7	1.9±0.5	

Data are expressed as mean±SD

Table 3. Linear correlation between Strain ratio (SR) and maternal and neonatal characteristics and labor outcome (secondary outcome)

	Correlation coefficient	p-value
Maternal age	-0.11	0.36
Pre-pregnant BMI	-0.16	0.17
BMI at delivery	-0.15	0.22
Number of previous VD	-0.15	0.21
Gestational Age at delivery	-0.13	0.31
Neonatal weight	0.01	0.91
Duration of labor	0.16	0.23
Cervical dilatation at CS	0.12	0.45

Figure legend

Figure 1. Strain Ration (SR) of uterine scar (Region 1) and surrounding myometrium (Region 2) obtained by using sonoelastography

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ABSTRACT

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This is a prospective cohort study conducted from February to September 2017 and including women with a previous planned or emergency CS $\geq$ 37 weeks' gestation performed 12 to 15 months before. Exclusion criteria were twin pregnancy, more than one CS, preterm CS, vertical CS, congenital uterine anomalies (ESHRE/ESGE classification of uterine anomalies: dysmorphic infantilis uterus, complete septate uterus, bicorporeal uterus, or hemi-uterus) [19], myomas and retroverted retroflexed uterus . Pregnant women were also excluded.

Management

Women underwent ultrasound examination using a 5.0- 7.0 MHz transvaginal probe (Esaote Mylab 60, Geneve, 5-8 MHz). Cervical measurements were performed with empty bladder and in dorsal lithotomy position placing the probe in the anterior fornix of the vagina and obtaining the visualization of the uterine scar and the sagittal view of the cervix. The uterine scar was identified as the thinnest and hyperechoi**c** zone at the site of the lower uterine segment.

Two regions of interest (ROI) of about 20-23 mm^2 were selected: uterine scar (Region 1) and surrounding myometrium (Region 2) in order to evaluate tissue strain after applying a 4-5 cycles of a perpendicular oscillatory pressure through rhythmic movements on the mid-sagittal plane. The myometrial ROI was placed in the middle part of the anterior uterine wall above the region of the previous uterine scar.

Acquired data were processed by an appropriate software (ElaXto®; Esaote S.p.A., Genova, Italy) and shown as different color zones ranging from red, yellow, green to blue from softer to harder tissues, respectively. The software automatically displayed a strain index for each ROI. The Strain Ratio (SR), was defined as Region 1 strain index/Region 2 strain index (Figure 1).

All values >1 indicate that the numerator (Strain Index of the scarred LUS) is greater (= harder) than the denominator (Strain index of the myometrium).

Outcome

An analysis of demographics, clinical characteristics, pregnancy and delivery outcome was performed within the study group.

The primary outcome of the study was to compare Strain Ratio (SR) among women who were grouped in accordance to the following characteristics:

- Presence or absence of previous vaginal delivery (VD)
- CS during or before labor
- Single or double layer of uterine suture
- Pyrexia during the post-partum period (>38°C)

The secondary outcome of this study was to evaluate the correlation between SR and the following characteristics: maternal age, maternal Body Mass Index (BMI), number of previous VD, gestational age at delivery, neonatal weight, duration of labor and cervical dilatation at CS.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 22 (IBM Inc., Armonk, NY, USA). Data were displayed as mean±standard deviation (SD) or as number (percentage). Categorical variables were compared using the Chi-square or Fisher exact test. Between-group comparison of continuous variables was undertaken using T-test and the Mann-

Whitney nonparametric equivalent test. Two-sided p-values were calculated and p values <0.05 were considered as statistically significant.

Being the SR a ratio between the Strain Index (SI) of the scarred LUS vs that of the intact myometrium, mean values ±DS >1 were assumed to indicate that the SI of the numerator was greater than that of the denominator and ultimately that the Scarred LUS was significantly stiffer than the intact myometrium. Using this approach, a significance test comparing the elasticity of the two uterine zones and yielding a p-value was not considered necessary.

Linear regression was used to assess the correlation between SR and maternal and pregnancy characteristics and correlation coefficients were expressed with corresponding significance levels. The study was performed following the STROBE guidelines [20]. This study has been approved by the local Ethics Committee.

RESULTS

Over the study period, 78 women were considered eligible for the study purpose. Of them, 5 were subsequently excluded due to the sonographic diagnosis of uterine anomalies, 4 were lost to follow up and 1 was pregnant at the time of the assessment. A total of 68 women with a mean interval-time from CS of 13.5±1.27 months were included in the final analysis; maternal and pregnancy characteristics are described in Table 1. The mean SR between the cesarean scar and the surrounding intact myometrium was 1.8±0.7. Overall, 59/68 (86.8%) of women had a CS during labor and 9/68(13.2%) during the second stage of labor at a mean gestational age of 39.6±1.3 weeks. The overall incidence of pyrexia during the post-partum period was 5.9% (4/68).

Table 2 describes the primary outcome of the study. No significant differences were found in terms of SR according to presence/absence of previous VD (1.56±0.45 vs 1.8±0.7; p=0.30), CS during labor (1.86±0.71 vs.1.7±0.; p=0.34), type of suture (single layer 1.7±0.6 vs double layer 1.9±0.8; p=0.13) or pyrexia during post-partum period (1.8±0.7 vs. 1.9±0.5; p=0.89). Strain Ratio was not correlated with the following maternal and labor characteristics: maternal age (p=0.36); pre-pregnant BMI (p=0.17); BMI at delivery (p=0.22), gestational age at delivery (p=0.31); number of previous VD (p=0.21); neonatal weight (p=0.91); duration of labor (0.23) and cervical dilatation at CS (p=0.45) (Table 3).

DISCUSSION

The main finding of our study is that the evaluation of uterine scar stiffness is feasible by using elastography. By means of this technique, we demonstrated that the stiffness of the uterine scar is higher than that of the surrounding myometrium and that the degree of scar stiffness is not correlated to the maternal characteristics, the intrapartum management nor the technique of uterine closure.

The hypothesis being tested is that histological changes characterizing uterine scar reparation after CS may be reflected by changes in its biomechanical properties. In particular, the higher stiffness, the reduced elasticity and tissue displacement during pressure could be determined by a lower density of smooth muscle cells and a higher collagen content [21,13].

While reproducibility studies have largely validated the use of elastography as standard technique to evaluate changes in cervical stiffness during pregnancy or induction of labor, data on the use of elastography in the assessment of LUS are lacking [14,15]. In literature there has been much interest on the sonographic antepartum assessment of the uterine scar whose features might predict the occurrence of uterine rupture or dehiscence in women with a previous Cesarean section undergoing a trial of labor.

Either the shape (scar asymmetry, wedge defects or ballooning in the LUS) and the thickness (6,9) of the scarred lower uterine segment have been sonographically investigated. A meta-analysis including 21 studies showed that there is a negative correlation between the LUS thickness and the risk of uterine rupture during subsequent trial of labor but it failed in identifying a cut-off with a good predictive value for uterine rupture mainly due to the heterogeneity of the included studies and to the lack of a standardized technique to measure LUS [6]. Some studies [22-25] have reported that the ultrasound characteristics of LUS during subsequent pregnancies may be influenced by a series of additional factors which are known to contribute to the occurrence of uterine rupture including maternal conditions, intrapartum management, techniques of uterine closure. On the other hand, recent evidences and experimental studies support the hypothesis that dehiscent or ruptured cesarean scars are characterized by an abnormal collagen content [26-28]. At the light of these observations the biomechanical properties of the lower uterine segment (LUS) in 33 women with a previous cesarean section (CS) have been assessed a few hours before repeated cesarean delivery by shear wave ultrasound (US) elastography [29]. In a few cases of this study high stiffness and restricted biomechanical resilience have been found in women with apparently normal scar and this has been proposed to explain the phenomenon of rupture during TOLAC despite a normal measurement of the LUS thickness at antepartum 2D ultrasound [26-29].

On the basis of our own data, biomechanical changes of the myometrial tissue due to the healing process at the level of the scar do not seem not to be influenced by maternal or previous pregnancy factors after an interval time of 12-15 months from CS. In this study we decided not to include pregnant women because we wanted to assess the pure effect of the previous cesarean surgery on the biomechanical properties of the lower uterine effect without the concomitant effect of other confounders such as a new pregnancy. Actually, although there is lack of data on that, we certainly envisage that the pregnant status may modify the elasticity of the uterine scar due to the related hormonal changes and to the morphological and volumetric changes of the uterus. We also decided not to include the women with retroverted/retroflexed uterus. The reason for this choice is that in this preliminary feasibility study we wanted to collect genuine and accurate data on the cesarean scar elasticity. Accordingly, we decided to exclude a priori cases of retroverted uterus because in these cases it may be difficult to insonate on the same plane and perpendicularly to the ultrasound beam the cesarean uterine scar and the surrounding intact myometrium. We cannot say that in retroverted uterus the elastography is not feasible simply because we have not tested it. However, we do not think that this is major issue as we envisage that the most promising clinical application of this technique may be the assessment of the cesarean scar elasticity in late pregnancy when the uterus is not retroverted

The prospective design, the originality in testing the sono-elastography on uterine scar and the standardization of the interval time from CS represent the main strengths of the present study. Potential confounding (ethnicity, maternal age, post-partum pyrexia) were all included in the analysis. The small sample size and the lack of evaluation of the intra and inter-observer variability are the main limitations of the study. Of course, this study does not draw conclusions on the correlation between biomechanical characteristics of uterine scar and subsequent risk of uterine rupture in a subsequent trial of labor due to the lack of follow-up data.

Conclusion

In conclusion, our study has shown that sonoelastography may provide reliable information about the stiffness of the cesarean uterine scar in non-pregnant women with a single previous cesarean delivery. The stiffness of the scarred LUS seems significantly increased compared with the surrounding intact myometrium but the degree of stiffness does not seem to be affected by previous obstetrical history or maternal characteristics. It is still to demonstrate if the use of sonoelastography during pregnancy and its combination with additional sonographic findings such as the thickness of the scarred LUS could help the clinicians in identifying those women at higher risk of uterine rupture during a trial of labor after CS.

Acknowledgments: none

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Table 1. Demographic characteristics and pregnancy outcome among 68 women with Casarean Section (CS)-uterine scar

Variables	n=68
Mean Strain Ratio (SR)	1.8±0.7
Maternal age	33.1±4.9
Caucasian	65(95.6)
Pre-pregnant BMI	23.5±3.7
BMI at delivery	28.0±3.7
Previous Vaginal Delivery	12(17.6)
Gestational Age at delivery	39.6±1.3
CS during labor	59(86.8)
CS during II stage	9(13.2)
Pyrexia during the post-partum period	4(5.9)

Data are expressed as mean±SD or n(%)

Table 2. Primary outcome

		p-value
Previous Vaginal Delivery		
Yes (n=12)	No (n=56)	0.30
1.56±0.45	1.8±0.7	
Cesarean Section during labor		
Yes (38)	No (n=30)	0.34
1.86±0.71	1.7±0.6	
Type of suture		
Single layer (n=43)	Double layer (n=25)	0.13
1.7±0.6	1.9±0.8	
Hyperpyrexia during Post-partum		
Yes (n=4)	No (n=64)	0.89
1.8±0.7	1.9±0.5	

Data are expressed as mean±SD

Table 3. Linear correlation between Strain ratio (SR) and maternal and neonatal characteristics and labor outcome (secondary outcome)

	Correlation coefficient	p-value
Maternal age	-0.11	0.36
Pre-pregnant BMI	-0.16	0.17
BMI at delivery	-0.15	0.22
Number of previous VD	-0.15	0.21
Gestational Age at delivery	-0.13	0.31
Neonatal weight	0.01	0.91
Duration of labor	0.16	0.23
Cervical dilatation at CS	0.12	0.45

Figure legend

Figure 1. Strain Ration (SR) of uterine scar (Region 1) and surrounding myometrium (Region 2) obtained by using sonoelastography

Reviewer #3

Authors study evaluates if elastography of a C-section scar is different from adjacent myometrium and if it is influenced by clinical characteristics of that prior delivery.
Novel use of elastography with possible important ramifications. However the study was essentially negative as defined by their purposes. Authors were able to conclude that elastography IS feasible and that the stiffness of the scar is higher than myometrium.

ABSTRACT:
Clear concise. Would consider adding "feasibility" to their purpose, as that is the first line of their conclusion.
Results and conclusion section seem to contradict - SR had no difference by clinical characteristics is listed in results. Conclusions state only that stiffness in scar is higher than myometrium (and does not correlate with characteristics). To consider adding that scar stiffness was different, into this results section, if space constraints allow as this is an important result.
R: We thank the reviewer for this comment that gives us the opportunity to improve our manuscript. Purpose and Result Sections of the abstract have been amended as follow:
"Purpose: to evaluate by means of elastography if the quantitative assessment of the cesarean scar elasticity is feasible using as reference the surrounding intact myometrium and to investigate if the cesarean scar stiffness is influenced by the clinical characteristics of the previous cesarean delivery.
"Results: 68 women were included. The mean SR was 1.8±0.7 thus indicating an increased stiffness of the uterine scar compared to the surrounding myometrium."

INTRODUCTION:
Last paragraph - include "feasibility" of performing this as an aim, since that is the authors initial conclusion.
R. Thank you. The last paragraph has been amended according to your suggestion
"The aim of our study was to evaluate by means of elastography if the quantitative assessment of the cesarean scar elasticity is feasible using as reference the surrounding intact myometrium and to investigate if the cesarean scar stiffness is influenced by the clinical characteristics of the previous cesarean delivery.

MATERIALS/METHODS:

First paragraph - used abbreviations that are not elswhere defined - ESHRE/ESGE. As many readers are not familiar with the classes by the descriptors used by the authors (U1b, for example), should consider using names, such as bicornuate, etc. Or listing anomalies that were included, if that is easier.

Why was retroverted uterus excluded? Is it because the measurement could not be accurately performed?

***R:* Thank you for this comment. We have listed the excluded uterine anomalies and changed the sentence accordingly:**

"ESHRE/ESGE classification of uterine anomalies: dysmorphic uterus, complete septate uterus, bicorporeal uterus, or hemi-uterus"

Moreover, your comment gives us the opportunity to clarify that in this preliminary feasibility study we wanted to collect genuine data on the cesarean scar elasticity and we actually decided to we decided to excluded those cases of retroverted and retroflexed uterus because in these cases it may be difficult to insonate on the same plane perpendicularily to the ultrasound beam the cesarean uterine scar and the surrounding intact myometrium. This has been now specified in the text

Management section, second paragraph "Real-time elastography..."

This paragraph should probably be moved elsewhere. Would consider the Introduction, near where authors detailed other organs for which elastography has been studied.

R. we thank the reviewer for this suggestion. We have deleted the second paragraph from the Management section. The technical principles of real time elastography are more appropriately described in the Introduction

In ABSTRACT and RESULTS, authors used "were finally included in the analysis" which should be changed to "were included in the final analysis."

R. thank you; the text has been amended accordingly

RESULTS:

Is there a p-values to show that difference between scar and myometrium was statistically significant? The discussion does discuss that it is higher, so this needs further detail to bulster this claim.

R: as described in Methods section, the sonoelastography is based on the concept that the elastic strain (also known as tissue elasticity) represents how a tissue distorts under a mechanic stress which is represented by the ultrasound beam. Stiffness is the complementary concept (high elasticity=low stiffness) The degree of stiffness (or elasticity) is quantified by the strain index. The greater is the stiffness. (in other words, the harder is the tissue and the lower is its elasticity or its deformability under the US beam) the higher is the strain index.
The strain ratio (SR), which is automatically provided by the ultrasound machine, is the ratio between the strain index of scarred LUS and the strain index of the intact myometrium. Being this parameter a ratio, all value >1 indicate that the numerator (in this case the Strain Index of the scarred LUS) is greater (=LUS harder) than the denominator (Strain index of the myometrium). So, the fact that strain ratio is 1.8 $\pm$0.7 is sufficient to claim that the stiffness of the uterine scar is higher than that of the surrounding myometrium. Since the Strain Ratio is >1, a significance test comparing the elasticity and yielding a p value is not needed. This clarification has been added to the text in the Methods section

DISCUSSION
Reiterating what is above. The first conclusions the authors draw is that the study is feasible. This is not mentioned in the Purpose, or aims, and if this is the initial conclusion, it should be.
R. thank you, based on the previous comments we have modified the first sentence of the discussion. (see reply above)

Additionally, the results given don't clearly support why it was feasible, although it can be inferred. Where all 68 women included, able to get the elastography performed? Authors mentioned retroverted uteri were excluded in the Materials, but none were listed as excluded in the results, which is surprising as this is relatively common.
Authors will need to temper the claim that this is feasible - will need to state what uteri it is feasible in. Particularly, is it possible in retroverted?

R: thank you for this smart comment. Among the 5 women excluded for “uterine anomalies” (see Results), 4/5 (4/78=5%) had retroverted retroflexed uterus. These cases were a priori

excluded from the study without proceeding to elastography. As stated above (and now specified in the text) the reason for this choice is that in this preliminary feasibility study we wanted to collect genuine and accurate data on the cesarean scar elasticity. Accordingly we decided to exclude those cases of retroverted and retroflexed uterus because in these cases it may be difficult to insonate on the same plane perpendicularly to the ultrasound beam the cesarean uterine scar and the surrounding intact myometrium. We cannot say that in retroverted uterus the elastography is not feasible simply because we have not tested it. However we do not think that this is major issue as we envisage that the most promising clinical application of this technique may be the assessment of the cesarean scar elasticity in late pregnancy when the uterus is not retroverted

As above - second line of discussion says that scar stiffness is higher than myometrium. Results don't necesarily support that - need a p-value or some other value to show the difference was significant.

R. thanks for this comment. As stated above, the strain index of CS scar and myometrium are not interesting data per se. What is clinically relevant is the relative stiffness of the two uterine areas and this is expressed by Strain Ratio (SR). So, the fact that strain ratio is 1.8 is sufficient to claim that the stiffness of the uterine scar is higher than that of the surrounding myometrium. Since the Strain Ratio is $>1 \pm 0.7$, a significance test comparing the elasticity and yielding a p value is not needed. This clarification has been now added to the text

Final paragraph of Discussion:

I don't think authors need to necessarily list the strengths of their article. They can point it out in the discussion where it is relevant to what is being discussed, but a general summing of strengths is not needed.

R. We respectfully disagree with the reviewer on this comment. At the bottom of a manuscript, a summary of the strengths and the limitations is usually suggested by the STROBE guidelines to assist the reader in a deeper comprehension of a scientific work

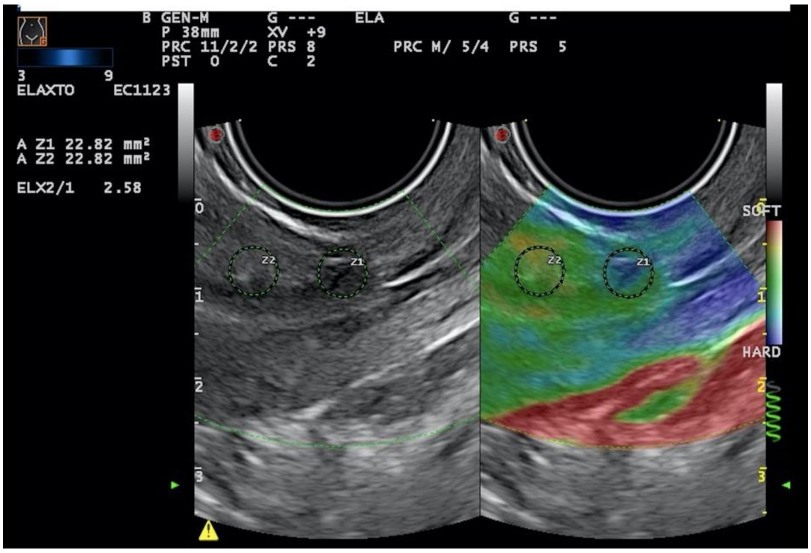
Final sentence "Of course, we cannot draw conclusion" - would change wording. Something along the lines of " This study does not draw conclusions...but should be evaluated in future research.

R. We thank the reviewer for this comment. The text has been amended accordingly.

FIGURE 1:

I don't see a figure 1

R. Figure 1 has been attached with the submission (figure legend is included in the main text). However, you can see Figure 1 below.



Click here to access/download;Figure;Figure elastosono R0.jpg

Highlights

- Ultrasound elastography provides information about the mechanical properties of tissues
- The evaluation of uterine scar stiffness is feasible by using elastography
- The stiffness of the uterine scar is higher than that of the surrounding myometrium
- The degree of scar stiffness is not correlated to the maternal characteristics and to the intrapartum management