Elastography for predicting preterm delivery in patients with short cervical length at 18-22 weeks of gestation: a prospective observational study

Zastosowanie elastografii w przewidywaniu porodu przedwczesnego u pacjentek z krótką szyjką macicy stwierdzoną między 18-22 tygodniem ciąży: prospektywne badanie obserwacyjnee

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Abstract

Objectives: *The aim of the study was to estimate the potential value of elastographic evaluation of the internal cervical os at 18-22 weeks of pregnancy in patients with short cervical length for prediction of preterm delivery (PTD).*

Material and methods: *This prospective observational study included 109 patients with cervical length of ⩽25 mm at 18-22 weeks scan. Stiffness of the internal cervical os was assessed by elastography. Elastographic assessment of the internal os was performed using a color map: red (soft), yellow (medium soft), blue (medium hard), and purple (hard). If two colors were visible in the region of the internal os, the softer option was noted. The following outcome measures were analyzed: percentage of PTDs in various categories of elastographic cervical assessment, sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of elastography in predicting PTDs. Additionally, ROC curves were constructed for elastography and cervical length for predicting PTDs.*

Results: *Forty-five cases of PTDs (<37 weeks of pregnancy) were found in the studied population. The number of PTDs was significantly higher in the red group, than in the blue and purple groups. The sensitivity, specificity, NPV and PPV for the assessment of both, red and yellow internal os for predicting preterm delivery were 82.2%, 75.0%, 84.0% and 72.5% respectively. The cut-off value for elastography suggested inclusion of both, red and yellow (warm) colors as predictors of PTD.*

Conclusions: *Elastographic evaluation of the internal cervical os at 18-22 weeks of pregnancy in patients with short cervical length may be useful in predicting PTD.*

Key words: **elastography** / **preterm delivery** / **short cervix** / **ultrasound** /

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Streszczenie

Cel: *Ocena znaczenia elastograficznej oceny ujścia wewnętrznego szyjki macicy w przewidywaniu porodu przedwczesnego (PTD) u pacjentek z krótką szyjką macicy stwierdzoną w 18-22 tygodniu ciąży.*

Materiał i metody: *Prospektywne badanie obserwacyjne obejmujące 109 pacjentek z długością szyjki macicy ≤25 mm stwierdzoną w 18-22 tygodniu ciąży. Elastograficznie oceniano twardość ujścia wewnętrznego szyjki macicy z użyciem następującej skali kolorów: czerwone (miękkie); żółte (średnio miękkie); niebieskie (średnio twarde); fioletowe (twarde). W przypadku uwidocznienia dwóch kolorów w okolicy ujścia wewnętrznego wybierano opcję bardziej miękką. Analizowano następujące zmienne: odsetek PTD w poszczególnych kategoriach twardości ujścia wewnętrznego oraz czułość, swoistość, ujemną i dodatnią wartość predykcyjną (NPV i PPV) elastografii w przewidywaniu PTD. Ponadto wyznaczono krzywe ROC dla elastografii i długości szyjki macicy w przewidywaniu PTD.*

Wyniki: *W badanej populacji wystąpiło 45 PTD (<37 tygodnia ciąży). Liczba PTD była istotnie większa w grupie czerwonej, niż w niebieskiej i fioletowej. Czułość, swoistość, NPV i PPV dla czerwonej i żółtej oceny ujść wewnętrznych wynosiła odpowiednio 82.2%, 75.0%, 84.0% i 72.5%. Punkt odcięcia dla elastografii sugeruje przyjęcie zarówno czerwonego jak i żółtego koloru jako czynników predysponujących do PTD.*

Wnioski: *Elastograficzna ocena ujścia wewnętrznego szyjki macicy w 18-22 tygodniu ciąży u pacjentek z krótką szyjką macicy może być przydatna w przewidywaniu PTD.*

Słowa kluczowe: **elastografia** / **poród przedwczesny** / **krótka szyjka** / **ultrasonografia** /

Introduction

Preterm delivery (PTD) is defined as birth before 37 completed weeks of pregnancy. PTD is responsible for 75% of all neonatal deaths [1]. Numerous attempts have been made to decrease its rate but, according to the World Health Organization, the incidence of PTD still exceeds 11% [2]. Early identification of patients at high-risk for PTD is crucial. Proper treatment and extending the pregnancy result in a major decrease in handicap and mortality rates [3–5].

Elastography is an ultrasound-based imaging technique used to estimate the stiffness of the visualized tissues. Three major types of elastography include: strain elastography (SE), acoustic radiation force impulse imaging, and shear-wave elastography [6]. In SE, the examined tissues respond to the applied force (either active or passive, i.e. due to respiratory or cardiovascular pulsation) by strain (higher in soft and lower in hard tissues). Finally, an elastogram is created, where areas of different colors represent various strain ratios, showing the stiffness of the examined areas. Possible applications of elastography were described in detail in recently published EFSUMB (European Federation for Ultrasound in Medicine and Biology) guidelines [7]. However, data on the use of elastography in obstetrics and gynecology are scarce. Previous studies showed the role of elastography in differential diagnosis of endometrial pathologies, and prediction of successful labor induction [8–11].

During the course of pregnancy, the increase of collagenolytic activity in the cervical tissue leads to a decrease of collagen content and modification of biomechanical properties of the cervix, and these changes may be identified by elastography [12]. A continuous reduction in cervical stiffness, with decreasing cervical length and increasing gestational age, was shown [13]. Excessive collagenolytic activity may lead to cervical insufficiency [12]. It was previously reported that it may be possible to assess the risk of preterm birth by means of elastography [14, 15].

The Aim

The aim of our study was to estimate the potential value of elastographic evaluation of the internal cervical os at 18-22 weeks of pregnancy in patients with short cervical length to predict spontaneous preterm delivery.

Material and methods

Study design

This prospective observational study investigated the potential of elastographic assessment of the internal cervical os for prediction of preterm delivery in patients with a short cervix observed during the 18-22 weeks ultrasound examination. The study was prepared and performed according to the STROBE Statement Checklist for observational studies.

Setting

This single-center study was conducted at the 3rd Chair and Department of Gynecology, Medical University of Lublin, Poland. Patients were recruited from May 2010 to August 2014.

Participants

Patients presenting for the routine second trimester ultrasound scan were included in the study. The inclusion criteria were: uncomplicated pregnancy, gestational age between 18+0 and 21+6 weeks; cervical length of ≤25 mm, viable singleton pregnancy, no uterine contractions, no evidence of preterm rupture of membranes, no cervical dilation, and no previous cervical surgery. The following data were recorded: elastographic color assessment of the internal cervical os and ultrasound cervical length, maternal age, obstetric history, and gestational age at delivery. In preterm deliveries the underlying cause was documented, cases due to maternal and fetal indications were excluded. All pregnancies were managed according to current guidelines. The flow chart of the study design is shown in Figure 1. The study was approved by the Local Bioethics Committee.

Written informed consent was obtained from all participants.

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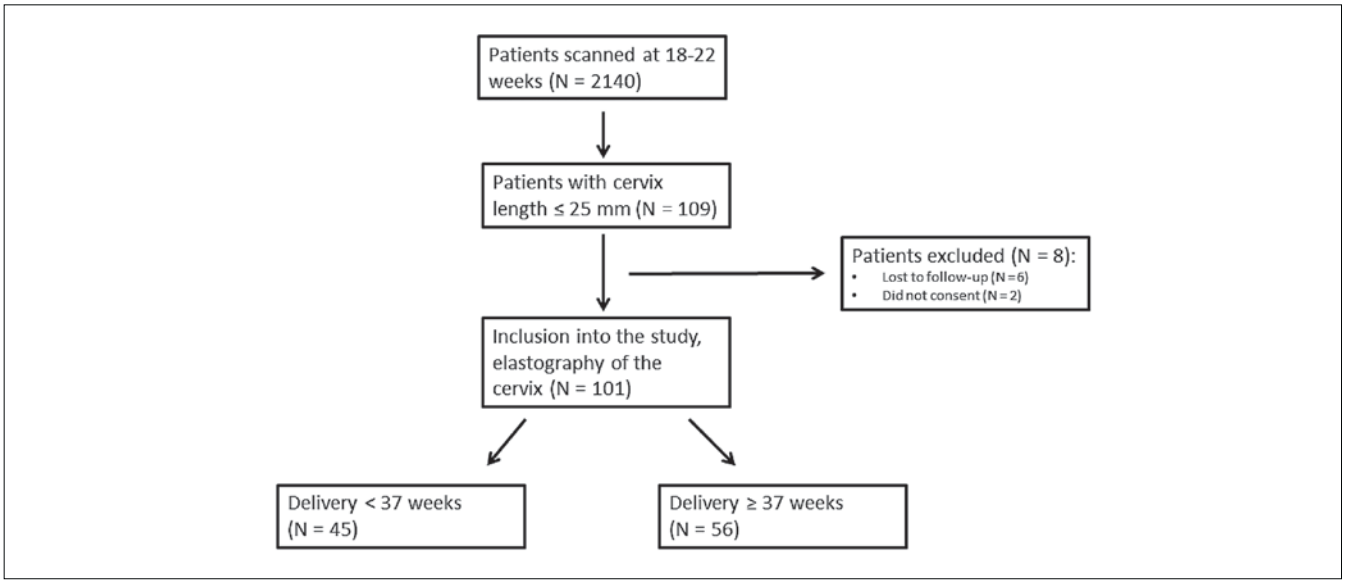

Figure 1. Flow chart of the study design.

Variables

The following data were recorded during the 18-22 weeks examination: maternal age, obstetrical history, cervical length (measured by ultrasound), and stiffness of the internal cervical os assessed by elastography. Patients were followed-up until delivery and gestational age at delivery was recorded.

The following outcome measures were analyzed: rate of PTDs in various categories of elastographic cervical assessment, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and positive and negative likelihood ratios (LR+ and LR-) with 95% confidence intervals of elastography in predicting PTDs. Additionally, ROC curves were constructed for elastography and cervical length in predicting PTDs.

Data sources/measurement

Physical examinations and management of pregnancies were performed by experienced obstetricians.

Ultrasound and elastographic examinations of the cervix were performed transvaginally by one experienced obstetrician (SW; 20 years of experience in ultrasound) on a Samsung Medison V20 Prestige, equipped with a 3D5-9EK transvaginal volume transducer (frequency range: 5 – 9 MHz, radius of curvature: 11.65 mm; field of view: 146 degrees; number of elements: 128, element pitch: 0.1964) with an Elastoscan® option.

Cervical length measurements were performed in the sagittal plane with the entire cervical canal visible, calipers placed on the internal and external os, with an empty bladder and minimal pressure [16]. Three measurements were performed and the shortest value was noted.

Elastography of the cervix was performed similarly to the technique reported by Swiatkowska-Freund and Preis [8]. The main difference in our study was the fact that we decided not to use the five-step elastography index proposed by Swiatkowska-Freund and Preis, and to evaluate the stiffness of the internal cervical os only. During the examination, the patients were breathing normally and the operator did not apply pressure to the cervix – the elastographic image of the cervix was generated by patient's breathing movements and arterial pulsation. After visualizing the sagittal section of the cervical canal, elasticity of the internal cervical os was assessed using a color map as: red (soft), yellow (medium soft), blue (medium hard) and purple (hard) (Figure 2). Any additional movements (patient changing position, coughing or even talking; the operator moving his hand) lead to the presence of artefacts and may change the appearance of the color map. Once a stable video sequence (at least 10 seconds) was obtained, the operator determined the dominant color of the internal cervical os. In case of difficulties (two colors of similar intensity visible) the softer option was noted.

Table I. Clinical characteristics of the studied population.

Patient age (median, range)	**28**	**19-43 (IQR 26-32)**
Obstetrical history No. of previous pregnancies (n, %) 0 1 2 3	 27 45 24 5	 26.7 44.5 23.7 4.9
History of preterm delivery (n, %)	49	48.5
Current pregnancy		
Cervical length at 18-22 weeks of gestation (median, range)	20	6-25 (IQR 16-23)
Cervical funneling at 18-22 weeks of gestation (n, %)	54	53.5%
Delivery before 32 weeks of pregnancy (n, %)	9	8.9
Delivery between 33 and 37 weeks of pregnancy (n, %)	36	35.6

Table II. Diagnostic accuracy of elastography performed at 18-22 weeks of pregnancy in predicting preterm delivery for various cut-off colors: red (soft); yellow and red (soft and medium soft) and red, yellow and blue (soft, medium soft and medium hard).

	Internal os elastography assessment		
	Red	Yellow and red	Blue, yellow and red
Sensitivity (95% CI)	68.9% (53.4-81.8)	82.2% (67.9-92.0)	95.6% (84.9-99.5)
Specificity (95% CI)	85.7% (73.8-93.6)	75.0% (61.6-85.6)	51.8% (38.0-65.3)
NPV (95% CI)	77.4% (65.0-87.0)	84.0% (70.9-92.8)	93.5% (78.6-99.2)
PPV (95% CI)	79.5% (63.5-90.7)	72.5% (58.3-84.1)	61.4% (49.0-72.8)
LR+ (95% CI)	4.82 (2.47-9.43)	3.29 (2.05-5.28)	1.98 (1.50-2.62)
LR- (95% CI)	0.36 (0.23-0.57)	0.24 (0.12-0.45)	0.08 (0.02-0.34)

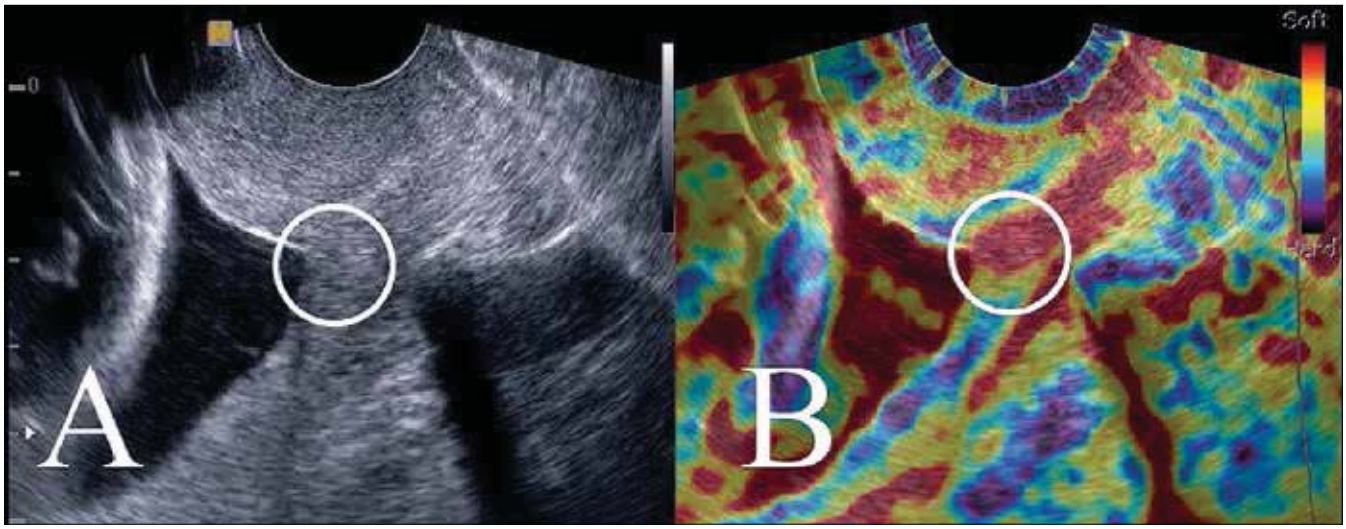

Figure 2. Gray-scale ultrasound (**A**) and elastography (**B**) of the internal cervical os (white circle). For elastography the following color map was used: red (soft), yellow (medium soft), blue (medium hard) and purple (hard). The internal cervical os was assessed as soft (red).

Statistical methods

Statistical analysis was performed using Statistica software (version 10, Statsoft, Tulsa, OK, USA). Frequencies of PTDs in various categories of elastographic cervical assessment were compared with the Kruskal-Wallis Anova. To determine the cut-off category of cervical elastography assessment in selecting high-risk for preterm delivery patients, we calculated the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and positive and negative likelihood ratios (LR+ and LR-) with 95% confidence intervals (CI) for red (soft); and red and yellow (soft and medium soft, warm colors) and red, yellow and blue (soft, medium soft and medium hard). Finally, ROC curves were constructed for elastography and cervical length. P value of <0.05 was considered as statistically significant.

Results

the flow chart of the study design is shown in Figure 1. Between 2010 and 2014, a total of 2140 patients presented for a routine 18-22 weeks ultrasound examination. In 109 patients the cervical length was <25 mm and these women were asked to participate in the study. Two patients did not consent and 6 were lost to follow-up leaving 101 cases for analysis. All patients were of Caucasian origin. The clinical characteristics of the studied population are shown in Table I.

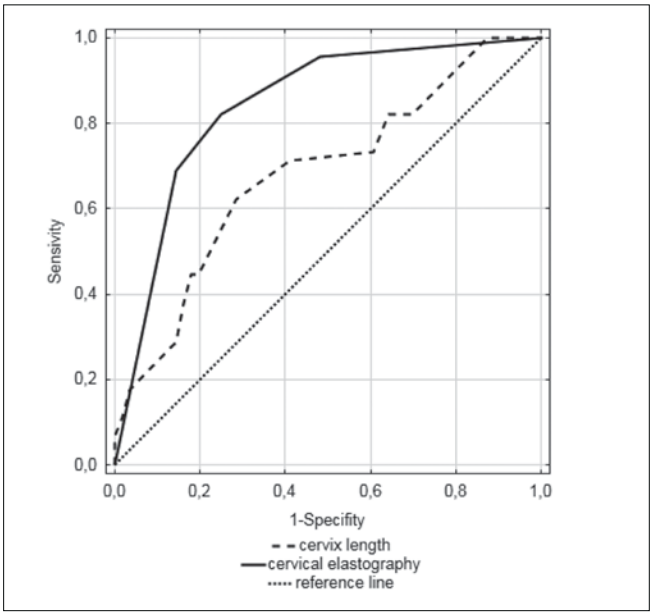

Figure 3. ROC curves for elastography and cervix length in predicting preterm delivery (<37 weeks of pregnancy).

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Forty-five cases of PTDs (<37 weeks of pregnancy) was found in the studied population: 33 in patients with a history of PTD and 12 in patients without a history of PTD. Out of these, 9 cases of PTDs (8.9% of the studied group) occurred <32 weeks of pregnancy: 8 in patients with a history of PTD and 1 in patients without a history of PTD.

At 18-22 weeks of pregnancy, the internal cervical os was evaluated as purple (hard) in 31, blue (medium hard) in 19, yellow (medium soft) in 12, and red (soft) in 39 patients. The numbers and rates of PTDs (<37 weeks of pregnancy) in the respective groups were: purple – 2 (5.1%), blue – 6 (31.6%), yellow – 6 (50.0%), and red – 31 (79.5%). The number of PTDs was not significantly different between purple and blue colors (cold colors) ($p>0.05$) and between red and yellow colors (warm colors) ($p>0.05$). The number of PTDs in the red group was significantly higher than in the blue and purple groups ($p=0.02$ and $p<0.001$), but not in the yellow group ($p = 0.74$). In all 9 cases of PTDs <32 weeks of gestation the cervix was assessed as red (soft) at 18-22 weeks of pregnancy.

In the warm color group (red and yellow) PTD occurred in 37 out of 51 patients (72.5%), whilst in the cold color group (blue and purple) – in 8 out of 50 patients (16.0%).

Spearman's correlation test showed a statistically significant correlation between cervical elastographic assessment and PTD (before 37 weeks of pregnancy) ($R = -0.62$; $p<0.05$).

The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and positive and negative likelihood ratios (LR+ and LR-) with 95% confidence intervals for various categories of internal os elastographic assessment in selecting patients at high risk for preterm delivery are shown in Table II.

ROC curves for elastographic internal os assessment and cervix length are shown in Figure 3. The cut-off value for elastographic cervical assessment suggested including bot, red and yellow (warm) colors as predictors of PTD, while the cut-off value for cervical length was calculated at 19 mm. The area under the curve (AUC) was 0.84 (95% CI 0.76 – 0.92) for elastography and 0.68 For cervical length (95% ci 0.58 – 0.79; P=0.02).

Discussion

Key results

Our results show that elastography allows to identify individuals at highest risk for PTD in the population of patients with a short cervix. Warm colors of the internal cervical os, red (soft) and yellow (medium soft), were identified as predictors of PTD. Interestingly, in patients with the cervical length of ≤25 mm, elastography was more accurate in predicting PTD than cervical length itself.

Generalizability

In our study, we included only patients with cervical length of ≤25 mm, but with no other symptoms of threatened PTD (uterine contractions, evidence of preterm rupture of membranes, cervical dilation, previous cervical surgery). Therefore, our results should be generalized only to asymptomatic patients, in whom a short cervix was an incidental finding during the 18 – 22 weeks ultrasound scan.

Limitations

We used the elastographic technique originally described by Swiatkowska-Freund and Preis [8]. We did not analyze the inter- and intra-observer variability, but due to the study design [all examinations were performed by one person) inter-observer variability could not be analyzed. The reproducibility and standardization of this technique has been questioned [17]. However, Swiatkowska et al., have recently shown satisfactory reproducibility and repeatability for this technique both, for experienced and inexperienced operators [18]. It has to be stressed that, regardless of the elastography technique used, all published papers present similar conclusions about the role of elastography in predicting PTD[14, 15, 19]. Finally, we assessed only the internal os of the cervix because we included only patients with short cervixes, and in such cases distinguishing many separate regions of the cervix could be problematic due to smaller area of the cervix. Moreover, Hernandez Andrade et al., observed that inter-observer agreement for elastography was highest in the internal os region [13]. Finally, it was shown that only the stiffness of the internal os predicted successful labor induction [8].

Interpretation

We demonstrated that it is possible to predict PTD using elastography. In previous studies the potential role of various elastographic techniques was assessed. Hernadez-Andrade et al., showed in a study of 189 unselected patients that elastographic cervical strain measurements at 16 – 24 weeks of gestation were significantly associated with the risk of PTD [19]. These authors also found that cervical strain seems to provide different information about cervical characteristics from cervical length. Swiatkowska-Freund et al., investigated a group of 44 patients admitted to the hospital due to contractions before 37 weeks of gestation and found that elastography index of the internal cervical os was strongly correlated with the risk of PTD [15]. In our previous study on 333 low-risk asymptomatic patients, we found that it was possible to identify patients with increased risk of PTD by means of elastography at 18–22 weeks of gestation [14]. Finally, Köbbing et al., showed that ultrasound elastography strain measurement of cervical stiffness is correlated with the predictability of PTD [20]. All these studies show the usefulness of elastography in predicting PTD using various elastography techniques in different populations. We further confirm these results and show that even in cases with a short cervix elastography may be of use in identifying patients with the highest risk for PTD. At present, screening for preterm delivery is based mainly on cervical length measurements. However, in a large study of 2915 patients the positive predictive value for PTD (<35 weeks of gestation) of the cervical length of ≤25 mm at 24 weeks of pregnancy was calculated at 17.8%, meaning that 82.2% of the patients with the cervical length of ≤25 mm delivered after 35 weeks of pregnancy [16]. This justifies the search for additional tests identifying patients at high risk for PTD – our results show that elastography may be a promising tool in this context. Additionally, this may explain the relatively poor performance of cervical length in predicting PTD in comparison to elastography in our study.

Conclusion

Elastographic evaluation of the internal cervical os at 18-22 weeks of pregnancy in patients with short cervical length may be useful in predicting spontaneous preterm PTD.

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