A Systematic Review of the Prediction of Preterm Birth Using Cervical Elastography
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Abstract

Background
Preterm birth is one of the major problems of the health system. There are still many questions that remain unanswered for researchers and there is a need for continuous research to improve the ability to predict and prevent preterm birth. The aim of the present study was to review cervical elastography studies in predicting the onset of preterm birth.

Materials and Methods: In this systematic review, to assess the prediction of preterm birth using cervical elastography, systemic search of online databases (Medline, Cochrane Central Register, EMBASE, Web of Science and Scopus complete) was done using the combination keywords of: (cervix uteri OR cervix) AND (elasticity OR elasticity imaging techniques OR elastography AND (preterm birth OR premature birth) up to Jun 2020. Study selection was done by two reviews.

Results: Elastographic evaluation of cervical os at 18-22 weeks of pregnancy is very useful in detecting patients at high risk for preterm birth in the population of asymptomatic women. Also, abnormalities detected in this technique, prior to clinical findings and ultrasound findings suggest the cervical shortening and funneling can predict the onset of preterm birth. As women with very short cervical length (CL<1.5 cm) may be completely asymptomatic, while elastography screening can be very effective in the management of prevention and treatment.

Conclusion
Elastographic evaluation of cervical os at 18-22 weeks of pregnancy is very useful in diagnosing patients at high risk for preterm birth in the population of asymptomatic women. However, there is a need for further research to investigate the role of elastography in predicting preterm birth.

Key Words: Cervical elastography, Prediction, Preterm birth.


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1- INTRODUCTION

Preterm birth is one of the major problems facing the health system and one of the important topics of annual reports. The prevalence of preterm births is estimated to range from 5 to 18% worldwide (1). Previous researches revealed that preterm births account for 75% of infant deaths, and despite efforts to reduce preterm births, World Health Organization estimates that 11% of all live births are preterm. Preterm births are associated with serious consequences such as cerebral palsy, developmental delay, and hearing and vision problems (2). Despite the poor prognosis of neonatal outcomes in preterm births before 37 weeks of pregnancy and subsequent adverse consequences that affect many families, diagnosing and managing women at risk for preterm birth has always been a priority for midwives and obstetricians (3).

A history of preterm birth is associated with its possible recurrence in the next pregnancy. However, there is a risk of experiencing preterm birth among about 90% of pregnant women without a previous history of such problem. Therefore, early detection and prevention of preterm birth is very important (4), because infants born at 23-32-weeks of pregnancy account for the highest rate of death and the incidence of severe neonatal disabilities and preterm birth has always been one of the important challenges of pregnancy specialists (5). Today, new diagnostic and therapeutic methods of preterm birth have reduced the rate of neonatal mortality by up to 35% and severe complications such as respiratory distress syndrome, sepsis, and long-term developmental defects by almost the same percentage (6). Preterm birth is diagnosed based on clinical criteria, including the occurrence of regular uterine contractions (more than 4 contractions within 20 minutes or 8 contractions within 60 minutes) with a contraction lasting for more than 40 seconds and 1-3 increase in cervical dilatation. Preterm rupture of the membranes and leakage of amniotic fluid are also important criteria for initiating preterm birth. Therefore, patients with these symptoms are classified in the preterm birth group and midwifery ultrasound will be performed to measure fetal dimensions (fetal biometrics), fetal adrenal glands, cervical length, and cervical elastography within 24 hours of admission (1). Imaging evaluation involves examining the size of the fetal adrenal glands and estimating the cervical softness and elasticity. The effect of fetal factor on fetal hormonal interactions, including the production of dehydroepiandrosterone sulfate (DHEAS), and the enlargement of the adrenal glands on ultrasound, as well as the cervical structural deformation towards softening and ripening, play a key role in initiating preterm birth. Researchers have taken into consideration the importance of cervical structural deformation in predicting the occurrence of preterm birth using cervical elastography as a new diagnostic technique (1, 7).

Cervical structural deformation occurs with a decrease in the composition of the collagen matrix. These changes can be detected using elastography ultrasound before cervical shortening. Cervical shortening is also a risk factor for preterm birth, which is commonly evaluated using transvaginal ultrasound (5). Elastography is an ultrasound-based imaging technique that shows soft tissue expansion by probe pressure in a color scheme. This technique has been widely used to evaluate the size and location of breast, thyroid, and prostate tissue tumors in biopsies. It has also been used in obstetrics and gynecology to predict labor induction and other differential diagnoses of gynecological diseases (8, 9). Color cervical elastography evaluates the condition of the internal cervical os and
the length of the cervix at 18-22 and 30 weeks of pregnancy. In this technique, degrees of cervical softness are reported with red (soft), yellow (somewhat soft), blue (somewhat stiff), and purple (stiff). However, the sensitivities of the above technique must be taken into account to achieve valid test results. Any additional movements such as a postural change, coughing, and talking by the patient would distort the results (5). On the other hand, an empty bladder is necessary to achieve a longitudinal view of the sagittal section and full view of the cervical canal despite the surrounding mucus. Since the cervical shortening and softening leads to preterm birth, cervical evaluation and measurement in the sagittal view is important in the prognosis of preterm birth. Tissue softness can be evaluated in elastography technique by applying a gentle pressure on the probe by the sonographer (3). Early detection and targeted interventions using preterm birth prediction techniques improve maternal and neonatal outcomes (10), therefore, cervical elastography has been considered. Advancements in imaging technology used to assess cervical changes along with clinical diagnoses of preterm birth have provided obstetricians with a powerful tool for estimating the risk of preterm birth; however, there are still many questions that remain unanswered for researchers and a need for continuous research to improve the ability to predict and prevent preterm birth is felt (10, 11). The aim of the present study was to review cervical elastography studies in predicting the onset of preterm birth.

2- MATERIALS AND METHODS

2-1. Method

In this systematic review, process of search was performed by two authors. Five online databases: Scopus, Cochran Central Register, Medline, EMBASE and Web of Science were searched using the combination keywords of: (cervix uteri OR cervix) AND (elasticity OR elasticity). Also, search was conducted without time and language restrictions up to Jun 2020 (Figure.1). Study selection was done by two independent reviews.

2-2. Eligibility criteria

Participants, interventions, comparators, and outcomes (PICO) model was used to as a search strategy tool to formulate the review objective and inclusion criteria in this review. Subjects were pregnant women. Relevant studies that applied ultrasound (US) elastography to assess cervical stiffness and predict preterm birth were selected. We considered the cervical length (CL) as a comparator.

2-3. Inclusion and exclusion criteria

We entered English published descriptive-analytical, prospective and, retrospective studies that assessed the prediction of preterm birth using cervical elastography. Moreover, all studies must have reported the results that had sufficient data regarding the diagnostic accuracy of cervical ultrasound (elastography). We also excluded review and meta-analysis, animal studies, letters to the editors and conference papers.

2-4. Study selection

Database search was done for possible studies, abstracts of the studies were screened for identification of eligible studies, full text articles were obtained and assessed and a final list of included studies was made. This process was done independently and in duplication by two reviewers and any disagreement was resolved by the 3rd reviewer.

2-5. Data extraction

We extracted information of each study using a form designed by research team including: author, year of publication, sample size, outcome measures tools and findings. Table.1 shows the clinical and
demographic characteristics of the studies included in this study.

2-6. Quality assessment

STROBE checklist for observational studies included 22 items. Quality of studies was used to assess study quality, some items are: objectives, study design, setting, bias, statistical methods, main outcome, limitations, interpretation and generalizability. This checklist assessed methodological quality. Total STROBE score ranged from 0-22. (12). Total STROBE results are shown in (Table.1); each study was independently assessed by two authors. Any discrepancies were discussed until a consensus was reached.

2-7. Synthesis of results

Due to the small number of studies and heterogeneous data, no meta-analysis was performed.

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**Fig.1**: PROSMA flowchart.
Table 1: Clinical and demographic characteristics of the studies included in this study and STROBE score (12).

<table>
<thead>
<tr>
<th>Study, Year Country, (Reference)</th>
<th>Study Design</th>
<th>Outcomes</th>
<th>Subject</th>
<th>Prediction value</th>
<th>Assessment tool</th>
<th>Results</th>
<th>STROBE score, Range: 0-22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal et al., 2018, India, (15).</td>
<td>Observational study</td>
<td>Role of ARFI technique and SWV estimates as a predictor of preterm birth and its comparison with other clinical and sonoelastographic measures.</td>
<td>34 women</td>
<td>Sensitivity and specificity (93% and 90%, respectively)</td>
<td>Sonoelastographic measures</td>
<td>Elastographic assessment of antenatal cervix is a novel technique of virtual palpation of internal os and can be utilized as an objective criterion for preterm birth prediction.</td>
<td>16</td>
</tr>
<tr>
<td>Hernández-Andrade et al., 2014, USA, (14).</td>
<td>Cross-sectional study</td>
<td>Association between low strain values in the internal cervical os, and lower risk spontaneous preterm delivery</td>
<td>189 women at 16-24 weeks</td>
<td>Endocervical: OR: 0.2; 5% CI: 0.03-0.96; entire cervix: OR: 0.17; 95% CI: 0.03-0.9.</td>
<td>Ultrasound elastography</td>
<td>There was significant association between Strain measurements in a view of the internal cervical os with sPTD, Strain values obtained from the external cervical os and from the sagittal view were not associated with sPTD.</td>
<td>17</td>
</tr>
<tr>
<td>Wozniak et al., 2014, Poland, (5).</td>
<td>Prospective observational study</td>
<td>Potential value of elastographic evaluation and spontaneous preterm delivery</td>
<td>333 women</td>
<td>Sensivity, specificity, NPV and PPV for both red and yellow internal os assessment in predicting preterm delivery were 85.7%, 97.6%, 98.3% and 81.1%, respectively.</td>
<td>Ultrasound scan</td>
<td>Elastographic assessment of the internal cervical os is associated with preterm delivery</td>
<td>19</td>
</tr>
<tr>
<td>Köbbing et al., 2014, Germany, (6).</td>
<td>Prospective study</td>
<td>Correlation between preterm delivery and ultrasound elastography strain measurement of cervical stiffness.</td>
<td>182 women</td>
<td>Rselective values &gt;0.89 were associated with preterm delivery with a sensitivity of 0.59 and a specificity of 0.86.</td>
<td>Ultrasound elastography</td>
<td>Ultrasound elastography strain measurement of cervical stiffness is correlated with the preterm delivery.</td>
<td>18</td>
</tr>
<tr>
<td>Hernández-Andrade et al., 2018, USA (13).</td>
<td>Prospective cohort study</td>
<td>Associated soft cervix and spontaneous preterm delivery.</td>
<td>628 women</td>
<td>sPTD &lt; 37 [relative risk (RR): 18.0 (95% confidence interval [CI]: 7.7-43.9), and P&lt;0.0001], and the sPTD&lt;34 [RR: 120.0 (95% CI: 12.3-1009.9), and P&lt;0.0001].</td>
<td>Ultrasound elastography</td>
<td>A soft cervix increases the risk of spontaneous preterm delivery.</td>
<td>17</td>
</tr>
</tbody>
</table>

ARFI: Acoustic Radiation Force Impulse, SWV: Shear wave velocity, sPTD: Subsequent spontaneous preterm delivery, OR: Odds ratio, RR: Relative risk, 95% CI: 95% confidence interval, PPV: positive predictive value.
3- RESULTS

Finally five studies were included in systematic review (Figure.1). In a prospective cohort study by Edgar Hernandez-Andrade et al., the women with a singleton pregnancy (n=628) were examined to measure the cervical length (mm), and softness [shear-wavespeed: (SWS) meters per second (m/s)] of the internal cervix. The results showed 12/628 (1.9%) subsequent spontaneous preterm delivery (sPTD)<34 and 31/628 (4.9%) sPTD<37 childbirths. The combined soft and short cervix caused an elevation in the sPTD<37 risk up to 18 times [relative risk (RR)=18.0 (95% confidence interval [CI]=7.7-43.9), and P<0.0001], and the sPTD<34 risk up to 120 times [RR=120.0 (95% CI=12.3-1009.9), and P<0.0001] in comparison with women having normal cervical length. The soft cervix alone caused an increase in the sPTD<37 risk up to 4.5 times [RR=4.5 (95% CI=2.1-9.8), and P=0.0002] and the sPTD<34 risk up to 21 times [RR=21.0 (95% CI=2.6-169.3); P=0.0003] in comparison with non-soft cervix. They concluded that the risk of sPTD <37 and sPTD <34 weeks of pregnancy was elevated by the soft cervix at 18-24 weeks of pregnancy, regardless of the length of the cervix (13).

Wozniak et al. employed a color map of red (soft), yellow (medium soft), blue (medium hard) and purple (hard) to assess the elastography of the internal os. Two colors visible in an area of internal os mean a softer option. The number of preterm births (<37 weeks gestation) was significantly lower in the blue and purple groups than in the red and yellow groups. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were 85.7%, 97.6%, 98.3% and 81.1%, respectively, to evaluate red and yellow internal os to predict preterm birth (5). In a cross-sectional study, the strain measurements showed a significant association between the internal cervical os and the sPTD. Women with strain values of less than the 5th centile had an 80% higher risk of sPTD than women with strain values of equal to and greater than the 25th centile in the endocervical canal (0.19), and in the entire cervix (0.14) [endocervical: odds ratio (OR)=0.2; 95% CI=0.03–0.96; entire cervix: OR=0.17; 95% CI=0.03–0.9]. The extent or statistical significance of these associations was not significantly changed by over-adjustment of body mass index (BMI) before pregnancy, maternal age, parity, smoking status, race, gestational age and past preterm childbirth. In this study, Strain measurements obtained in a cross-sectional view of the internal cervical os were significantly associated with sPTD. But Strain measurements obtained from the external cervical os and from the sagittal view were not associated with sPTD (14).

In a study by Agarwal et al., the pregnant participants with gestational age of 28–37 weeks (n=34) showing signs of preterm labor were examined by modified Bishop’s score, cervical length by ultrasound (US), ARFI to derive Elastography index (EI), and shear wave velocity (SWV) of the cervix. According to their results, 20 patients had a term delivery with gestational age of >37 weeks and 14 patients had a preterm delivery. Based on receiver operating characteristics (ROC) curves, the maximum sensitivity and specificity (93% and 90%, respectively) were found for the SWV to predict the preterm birth with the cutoff point of 2.83m/s. They concluded that the elastography index (EI) was comparable to the modified Bishop’s score, but both had less sensitivity (15). Köbbing et al. investigated 8928 regions of interest (ROIs), and 6696 ratios, with the median gestational age of 26±6.1 weeks, the median maternal age of 33±5.6, and the medial parity of 1±0.9 at the baseline. The range of intra-class-correlation was
between 0.893 and 0.967 in validation phase. According to the results, the sPTD prevalence was reported to be 11.9% and the best preterm birth predictor was introduced as the strain ratio Rselective, with the Rselective values of >0.89 associated with preterm birth with a specificity of 0.86 and a sensitivity of 0.59 (OD=1.474 for an elevation of 0.1 in Rselective; P=0.002), (6).

4- DISCUSSION

The elastography technique has received much attention in the diagnosis of preterm birth. Findings of the Hernandez-Andrade’s study (2014) revealed a weak correlation between the strain value index and the six cervical regions with cervical length, however, strain elastography measurements in a cross-sectional view of the internal cervical os showed a significant relationship with the incidence of preterm birth. There was a significant relationship between strain value ≤ 25th percentile in the endocervical canal and along the cervix with preterm birth despite controlling the effect of interfering factors such as gestational age, maternal age, history of preterm birth, maternal smoking status, number of deliveries, and body mass index (BMI) before pregnancy, while there was no relationship between the strain value index obtained from the external cervical os with the incidence of preterm birth (14).

Evaluation of cervical structural characteristics such as deformity, ultrasound attenuation, cervical elongation, and collagen band composition are important in predicting preterm birth; however, studies have reported different features for cervical tissue throughout its length and completely different features for the external cervical os (14, 16). Another study by Hernandez Andrade et al. (2018), using transvaginal ultrasound shear wave elastography between 18-24 weeks of singleton pregnancies, referred to cervical softness and shortening as two risk factors for preterm birth before the 34th week of pregnancy, and independent from cervical shortening, cervical softness was regarded as an important factor in initiating preterm birth (13). Evaluation of the elastic properties of the cervix provides important information in predicting preterm birth. In this regard, shear wave-based elastography provides more reliable results than ultrasound elastography considering the fact that it does not depend on the skill of the experimenter in the field of cervical elasticity. Besides, shear wave-based elastography provides more accurate prediction of preterm birth in the internal cervical os than the external cervical os despite the distribution of its collagen network (17). In this technique, cut-off value is the 25th percentile for determining cervical softness (13). Agarwal et al. (2018) investigated the biometric accuracy of fetal adrenal glands and dynamic cervical elastography by comparing useful indices in predicting preterm birth. The study reported that cervical ultrasound elastography had the highest sensitivity (96.7%), and specificity (87%) in predicting preterm birth. This index also showed a strong relationship with fetal adrenal gland size as a valid index in predicting preterm birth. However, the limitation of this study included the fact that cervical condition was evaluated using abdominal ultrasound (1).

Wozniak et al. (2014) showed the ability to evaluate preterm birth in 18-22 weeks of pregnancy using elastography with color spectrum differentiating soft and hard tissues with warm colors (red and yellow) for soft tissue and cervical length at the 30th week of pregnancy. According to the results of this study, cervical elastography, especially in the internal cervical os, showed a stronger association with the incidence of preterm birth in pregnant women in the low-risk group compared to the cervical length assessment (5).
Köbbing et al. (2014) referred to the application of elastographic diagnostic technique throughout pregnancy. Strain value index difference was evident in differentiating soft and hard areas of cervical tissue and structural difference in cervical tissue throughout pregnancy. However, measuring cervical length along with assessing cervical structural changes had better diagnostic value in predicting preterm birth (6). Agarwal et al. (2018) demonstrated the use of ultrasound dynamic elastography for cervical assessment during pregnancy. Acoustic radiation force impulse (ARFI) technique was also found to be useful in predicting the risk of preterm birth. This study also referred to cervical length of ≤ 25 mm as a diagnostic criterion for preterm birth (15). The results of previous studies have pointed out the importance of static and dynamic elastography methods in the diagnostic study of preterm birth. However, the dynamic technique has been regarded as a more suitable method for differentiating soft and hard areas of cervical tissue during pregnancy considering the penetration velocity of shear waves and the lack of dependence on the pressure transducer (18).

Nevertheless, elastography, especially shear-wave dynamic technique is known as a more useful perinatal diagnostic tool in assessing the risk of preterm birth as compared to fetal adrenal biometry and cervical length measurement. It should be noted the above studies have limitations such as small sample size, examination of singleton and mostly nulliparous pregnancies, and the use of transabdominal probes (1). According to the recommendations of the National Institute for Health and Care Excellence (NICE) on the use of transvaginal ultrasound as a diagnostic test for preterm birth, despite its more invasive nature compared to transabdominal ultrasound, it seems necessary to carry out further studies (19).

4-1. Study Limitations
It was not possible to carry out meta-analysis considering the small number of studies. Some of the studies reviewed in the present systematic review had low methodological quality. Future studies should be designed and reported based on STROBE checklist. Other limitations of the present study include the small number of studies and their low sample size, which indicates the need for further studies with a larger sample size in this field. The results of some studies with low sample sizes may change if the sample size increases.

5- CONCLUSION
Elastographic evaluation of the internal cervical os at 18-22 weeks of pregnancy can be valuable in diagnosing pregnant women preterm birth in the asymptomatic female population. There is a need to perform further research on relationship between elastographic parameters in predicting preterm birth. The cost-effectiveness of this method should also be evaluated in future studies.

6- CONFLICT OF INTEREST: None.

7- REFERENCES


