Quantitative Elastography of the Cervix for Predicting Labor Induction Success

Quantitative Elastografie des Gebärmutterhalses zur Vorhersage einer erfolgreichen Geburtseinleitung

Abstract

Purpose: To evaluate the role of quantitative elastography of the cervix in the prediction of successful labor induction compared to the Bishop score (BS) and ultrasound cervical length (CL).

Materials and Methods: A prospective pilot study was conducted between July 2010 and June 2011 in patients without preterm membrane rupture undergoing labor induction with vaginal prostaglandins. Before starting induction, the BS, functional CL and cervical tissue strain (TS) were assessed. TS assessment was performed twice using the Tissue Doppler Imaging (TDI) software. Diagnostic accuracy was evaluated for the prediction of the following endpoints: active labor achievement (success vs. failure, time interval <24 h and <48 h), vaginal delivery (success vs. failure, time interval <36 h and <72 h) and total amount of prostaglandins used for labor induction (<6 mg and <12 mg).

Results: We analyzed 77 patients with a mean gestational age of 39.7 ± 1.5 weeks of gestation and a mean strain of 0.75 ± 0.17. The TS significantly predicted a failure of labor induction, which occurred in 4 cases, both in mono- and multivariate analysis. No correlation was found between the TS and other outcomes. The Bishop score and functional cervical length were found to predict only an early response to labor induction (time to active labor <24 h, time to vaginal delivery <36 h and PG usage <6 mg). The diagnostic accuracy was slightly but not significantly improved if both TS and CL were considered.

Conclusion: Preliminary data show the possible usefulness of quantitative cervical elastography in the prediction of labor induction failure.

Zusammenfassung

Ziel: Untersuchung der Rolle der quantitativen zervikalen Elastografie im Vergleich zum Bishop-Score (BS) und zur sonografischen Zervixlänge (CL) in der Vorhersage einer erfolgreichen Geburtseinleitung.


Ergebnisse: Es wurden 77 Patientinnen mit einem mittleren Gestationsalter von 39,7 ± 1,5 Schwangerschaftswochen untersucht. Der mittlere TS betrug 0,75 ± 0,17. Der TS sagte signifikant ein Versagen der Geburtseinleitung, welches in 4 Fällen aufgetreten ist, unabhängig von der CL, voraus (TS 0,6±0,1). Es wurde keine Korrelation zwischen TS und andere Ergebnisse festgestellt. Der BS und die CL konnten nur eine frühzeitige Antwort auf eine Geburtseinleitung vorhersagen (Zeit bis zur aktiven Geburtsphase <24 Std., Zeit bis zur vaginalen Entbindung <36 Std. und PG-Nutzung <6 mg). Die diagnostische Genauigkeit unter Berücksichtigung des TS und der CL konnte leicht, aber nicht signifikant, verbessert werden.

Schlussfolgerungen: Die vorläufigen Daten zeigen einen möglichen Nutzen der quantitativen zervikalen Elastografie in der Vorhersage einer frustranen Geburtseinleitung.
Introduction

Tissue Doppler Imaging (TDI) is a new Doppler-based tool for the imaging and quantitative estimation of tissue elasticity by ultrasound. TDI enables the tracking of tissue displacement, whereas the quantification of tissue deformation (strain) occurs using the TDI-Q (Tissue Doppler Imaging-Quantification) software [1 – 3]. Tissue strain can be expressed as Lagrangian or natural strain. The Lagrangian strain describes the deformation (ε) of an object with its length L(t) relative to its initial length L(t0) \(\varepsilon = (L(t) - L(t0))/L(t0)\), whereas the natural strain is based on the temporal integration of the instantaneous deformation (dε) of the tissue \(\int \varepsilon dt\) \(\varepsilon = (L(t+dt) - L(t))/L(t)\) \[4\]. For a small deformation, the natural and Lagrangian strains are similar, whereas for a larger deformation (>10 – 15 %, as induced in this study), the natural strain is thought to be more appropriate. Using the tissue velocity approach and based on Doppler ultrasound, the natural strain rate (i.e., the speed of deformation) is calculated as the spatial derivative of the local tissue velocities. The natural strain is subsequently calculated as the temporal integration from the onset to the end of the compression cycle \[5\]. The estimation of tissue stiffness occurs by measuring the cervical tissue deformation (strain) during the movement of compression of the cervix, which is manually induced by the vaginal probe. Standardization of the applied force is provided by exerting movements until maximum compression of the anterior cervical lip is achieved, while taking care to avoid lateral and longitudinal dislocation of the tissues. Under standardized conditions for the acquisition of raw data and the strain calculation, strain measurement has proved to be feasible and highly reliable \[6, 7\].

The aim of our study was to evaluate the diagnostic accuracy of cervical tissue strain (TS) assessment in predicting successful labor induction. The diagnostic accuracy of TS assessment was compared with the accuracy of the Bishop score, digital cervical consistency assessment according to the Bishop score and cervical length measurement by ultrasound. The intra-operator reliability of TDI-based cervical elastography was also evaluated.

Methods

Setting and study design

The prospective cohort study was conducted in a regional hospital setting (Frauenklinik, Mathias-Spital Rheine, Germany) between July 2010 and July 2011. The study was designed according to the Declaration of Helsinki and was approved by the local Ethics Board. Informed consent was obtained at the time of enrollment.

Study population

Eligibility criteria: We included patients with singleton pregnancies who underwent labor induction with vaginal prostaglandins on medical indication. Further inclusion criteria were the following: absence of uterine contractions (<4 contractions per hour), functional cervical length ≥1.5 cm by ultrasound, Bishop score <7, absence of spontaneous, premature rupture of membrane (PROM) at admission.

Exclusion criteria: Patients were excluded from the study population in the case of early, voluntary abandon of labor induction or secondary caesarean section, which occurred before one or more of the considered outcome measures could be evaluated (<12 hours after beginning induction and use of a single dose of PG) or before one of the considered outcomes could be evaluated (Fig. 1: Study population).

Interventions

At the time of hospitalization for labor induction, the obstetrical and gynecological history was acquired and an admission cardiotocography (CTG) was taken to assess whether uterine contractions were present and to assess the fetal heart rate pattern. A transvaginal ultrasound scan was executed just before digital examination and labor induction by a single experienced gynecologist. Ultrasound was performed using a 9–MHz vaginal probe (Aplio XG Ultrasound System, Toshiba Medical Systems). The total and functional cervical lengths were assessed. Real-time cervical elastography was performed and one raw dataset was acquired by the same operator twice (for a total of two raw datasets per patient). Results were blinded to any previous digital examination findings.

The cervical length was measured with a continuous line connecting the internal cervical orifice with the external one. If funneling was present, only the residual cervical length was measured and funneling was not included in the measurement (functional cervical length) \[8\].

Real-time cervical elastography was performed by the same operator using the Tissue Doppler Imaging (TDI) tool as previously described \[6\]: Two homogeneous freehand movements of compression and subsequent decompression of the cervix were exerted by means of a vaginal transducer. Movements were directed perpendicular to the longitudinal axis of the cervix, thus avoiding lateral dislocation. The compression had to be sufficient to obtain maximal compression of the anterior portion of the cervical tissue (until the start of dislocation of the posterior part of the cervical lip without further compression of the anterior lip). A five-second loop including both cycles of movements was acquired and stored in the machine as raw data. The procedure was then immediately repeated in order to acquire two raw datasets for each patient.

A digital cervical examination was performed just before the beginning of induction by an experienced midwife or gynecologist (with at least 3 years experience), who was blinded to the results of the cervical ultrasound examination, describing cervical effacement, position, consistency and dilatation, as well as the station of the fetal head in the pelvis. The Bishop score was then calculated for a score ranging from 0 to 10 \[9\].

Labor induction was performed exclusively with Dinoprost prostaglandin (Minprostin® E2). Its formulation was 3 mg vaginal tablets, 2 or 1 mg vaginal gel or a 0.5 mg intracervical gel. The type of formulation and the interval between prostaglandin applications were decided by the obstetrical team under consideration of the frequency and intensity of uterine contractions, cervical status and fetal-maternal wellbeing.

Finally, a raw data evaluation and strain calculation were performed after termination of patient recruitment and were blinded to the results of labor induction. Raw data were evaluated offline by the gynecologist using TDI-Q commercial software (Tissue Doppler Imaging Quantification, Toshiba Medical Systems) as natural strain as previously described \[6\]: A circular ROI (region of interest) was placed on the entire thickness of the anterior portion of the cervix during the cycle with the greater tissue excursion. The strain was calculated by the software by selecting the interval between a frame of maximal compression and one of maximal relaxation (Fig. 2). The natural strain was used to describe the deformation occurring during the compression...
movement. The two different raw datasets acquired for each patient were analyzed at intervals of at least one day. The mean value of the two measurements of cervical TS was used to evaluate the accuracy of this technique for predicting the selected outcomes.

Data collection
Data about pregnancy course and outcomes were recorded in the clinical files of the patients (View-Point System, GE Healthcare, and patient medical records). The following outcome measures were reported: timing of active labor (cervical dilatation ≥ 3 cm and presence of regular uterine contraction), timing and type of delivery as well as dosage and formulation of prostaglandin used. The data were analyzed after the termination of patient enrollment and were blinded to the results of pre-induction cervical features.

Outcome measures
We evaluated the following outcome measures: **success of labor induction** (successful achievement of labor versus failed labor induction), **time interval to labor** (< 24 hours and < 48 hours), **success of vaginal delivery** (successful achievement of vaginal delivery versus cesarean delivery), **time interval to delivery** (< 36 hours and < 72 hours), as well as **total mg of PG used** for labor induction (< 6 mg and < 12 mg). Active labor was defined as the presence of uterine contractions accompanied by cervical dilatation ≥ 3 cm [10]. Labor induction was considered to have failed when a cesarean delivery was indicated after unsuccessful labor induction because of a lack of cervical ripening progress. According to the internal rules of our hospital, it should occur after at least 72 hours and 12 mg of prostaglandin application or, alternatively, in the case of regular uterine contraction failing to achieve cervical dilatation ≥ 3 cm.
Available TDI-Q software preset functions: in our case the ROI tracking function and natural strain preset were selected. The frame of maximal compression of the cervix is identified and the beginning phase of relaxation is defined (arrow in the middle). The frame of maximal relaxation after the compression of the cervix is defined (arrow in the middle). A circular region of interest (ROI) is placed on the full thickness of the anterior part of the cervix (dotted circle). This corresponds to a phase of maximal relaxation of the tissue after maximal compression through the vaginal probe was manually induced. Strain is then automatically calculated by the software by selecting the button “strain” (arrow on the left) and the tissue deformation value is indicated: as a function of the time during the movement of relaxation (arrows at the top on the right), and as the maximal strain value obtained (circled down on the right).
Statistical analysis
Data were analyzed using R (version 2.14.1) and p < 0.05 was considered significant. Data were presented with the median value and the interquartile range (IQR), with the mean value and its standard deviation, with prevalence and absolute values, or reference value and 95% confidence intervals. The intra-observer agreement for cervical TS measurement among the two measurements was evaluated by means of the Intraclass Correlation Coefficient (ICC). The mean value of the two measurements of cervical TS was used to evaluate the accuracy of the technique for predicting the selected outcomes. The correlations were evaluated by means of the Spearman’s correlation test. The Kruskal-Wallis test and the one-way ANOVA for continuous variables were used for variance analysis where suitable. The chi-square test was used for the comparison of multiple categorical variables. The accuracy for predicting the considered outcomes in every diagnostic method studied (Bishop score, ultrasound cervical length and elastography cervical TS) was tested using ROC (Receiver-Operating-Characteristics) curves and the area under the curve (AUC) values. Moreover, we compared AUCs using the De Long’s test for two correlated ROC curves.
We considered STARD (Standards for Reporting of Diagnostic Accuracy) criteria for accurate reporting of studies on diagnostic accuracy tests.

Results

Description of the study population
During the study period, 86 patients were considered eligible and were admitted for planned medical induction of labor between June 2010 and June 2011. Nine patients were excluded: four of them because of a Bishop score ≥7, 3 due to induction interruption because of maternal incompliance, and 2 because of induction-related complications (pathologic fetal CTG) (Fig. 1: Study population). A total of 77 patients were included in our analysis. No adverse event of pre-induction diagnosis was registered. A total of 77 patients were included in our analysis. We performed an analysis of the correlation between cervical TS and functional cervical length by Spearman’s correlation test. The Rho result was −0.154 (longer cervix was associated with lower strain – less elastic cervix) but it was not statistically significant (p 0.196). We also found positive correlations between cervical TS and gestational age (less elastic cervix correlated with early gestational age), even if not statistically significant. No difference was recorded between cervical TS and cervical consistency evaluation in the Bishop score (less elastic cervix correlated with a firm consistency in the Bishop score).

Ultrasound TS and other pre-induction cervical features
The mean values for pre-induction cervical features are shown in Table 1. We performed an analysis of the correlation between cervical TS and functional cervical length by Spearman’s correlation test. The Rho result was −0.154 (longer cervix was associated with lower strain – less elastic cervix) but it was not statistically significant (p 0.196). We also found positive correlations between cervical TS and gestational age (less elastic cervix correlated with early gestational age), even if not statistically significant. No difference was recorded between cervical TS and cervical consistency evaluation in the Bishop score (less elastic cervix correlated with a firm consistency in the Bishop score).

Table 1 Population features.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value (± standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mother’s age at delivery (years)</td>
<td>29.7 (± 3.5)</td>
</tr>
<tr>
<td>primiparous</td>
<td>58% (45/77)</td>
</tr>
<tr>
<td>gestational age at delivery (weeks)</td>
<td>39.7 (± 1.5)</td>
</tr>
<tr>
<td>pre-induction features</td>
<td></td>
</tr>
<tr>
<td>Bishop score value</td>
<td>3.7 (± 1.4)</td>
</tr>
<tr>
<td>cervical consistency (Bishop)</td>
<td>1.26 (± 0.68)</td>
</tr>
<tr>
<td>cervical length (mm)</td>
<td>30.3 (± 8.3)</td>
</tr>
<tr>
<td>functional cervix length (mm)</td>
<td>28.1 (± 8.5)</td>
</tr>
<tr>
<td>cervical TS</td>
<td>0.75 (± 0.17)</td>
</tr>
<tr>
<td>induction indication</td>
<td></td>
</tr>
<tr>
<td>prolonged pregnancy</td>
<td>35% (27/77)</td>
</tr>
<tr>
<td>fetal growth restriction</td>
<td>13% (10/77)</td>
</tr>
<tr>
<td>late preeclampsia</td>
<td>10% (8/77)</td>
</tr>
<tr>
<td>maternal indication</td>
<td>10% (8/77)</td>
</tr>
<tr>
<td>fetal macrosomia</td>
<td>8% (6/77)</td>
</tr>
<tr>
<td>glucose metabolism alterations</td>
<td>7% (5/77)</td>
</tr>
<tr>
<td>oligohydramnios</td>
<td>7% (5/77)</td>
</tr>
<tr>
<td>other indications</td>
<td>10% (8/77)</td>
</tr>
</tbody>
</table>

Prevalence with absolute values, mean (± standard deviation).

Ultrasound TS and other pre-induction cervical features
The mean values for pre-induction cervical features are shown in Table 1. We performed an analysis of the correlation between cervical TS and functional cervical length by Spearman’s correlation test. The Rho result was −0.154 (longer cervix was associated with lower strain – less elastic cervix) but it was not statistically significant (p 0.196). We also found positive correlations between cervical TS and gestational age (less elastic cervix correlated with early gestational age), even if not statistically significant. No difference was recorded between cervical TS and cervical consistency evaluation in the Bishop score (less elastic cervix correlated with a firm consistency in the Bishop score).

Pre-induction cervical features and outcome measures
We evaluated the differences for pre-induction features in terms of chosen outcomes: induction failure, time interval to active labor, mode of delivery, time interval to delivery, total milligrams of PG used for induction (Fig. 1, Table 2). We found a longer cervix to be associated with a significantly longer time to delivery and higher prostaglandin usage (p < 0.05). We found a significantly lower Bishop score to be associated with a longer time to delivery (p < 0.05). Finally, significantly lower cervical elastography TS values were associated with a failure of medical labor induction (p < 0.05). All four cases of medical induction failure were primiparous and presented significantly lower TS values in comparison with both successful induction subgroups of primiparous and pluriparous patients (p < 0.05), as shown in Fig. 3.
Considering only the outcome of successful medical inductions of labor we presented the characteristics of the women divided into...
three groups: failed induction (all primiparous), successful induction in primiparous women, successful induction in pluriparous women (Table 3). We found a significantly earlier gestational age in the failed induction group and a longer, functional cervical length. Moreover, in the failed induction group we found significantly higher prostaglandin usage and longer time to delivery than in the successful labor induction groups. In Table 4 we also performed a multivariate logistic regression analysis using the logarithmic transformation of cervical elastography TS and we found a low value to be a risk factor for the failure of the medical induction of labor in all our populations and in the primipar-
cesses of motion (such as using arterial or respiratory motion), or by evoked extrinsically, for example, by exploiting the internal sources tissue stiffness, deformation (also called strain) can be tracked during deformation. In order to assess outcomes was always above 50%, whereas the AUC value of cervical consistency in the Bishop score was under 50% (not shown) among all outcomes except for labor induction success. We tested the combination of cervical length and elastography. This only slightly, but not significantly, improved the diagnostic accuracy of the tool (data not shown).

Discussion

Tissue elastography has already been successful introduced in several fields of medicine [11–14]. This sonographic tool enables the tracking of tissue motion during deformation. In order to assess tissue stiffness, deformation (also called strain) can be evoked extrinsically, for example, by exploiting the internal sources of motion (such as using arterial or respiratory motion), or by manually applying an extrinsic force to the tissue via the transvaginal probe. Some recent publications show the possible application of this new technology for the evaluation of the cervix during pregnancy [15, 16]. Swiatkowska-Freund first described the elastographic pattern of cervical tissue caused by the movement generated on the cervix by the patient’s breathing and arterial pulsation [17]. Nonetheless, the proposed method allows only a semiquantitative and subjective evaluation of the strain generated in the cervix by the patient’s breathing and arterial pulsation. Furthermore, the study was conducted on a small number of patients (only twenty-nine), and the operator independency of the process of acquisition of the elastographic images was not reported to have been tested.

Recently, Molina reported a reliability study on the evaluation of quantitative elastography of the cervix during pregnancy [18]. Similarly to our method, strain calculation is based on freehand compression of the cervical tissue. Here, even if the method is described as semiquantitative, the author showed that cervical tissue strain was more strongly associated with cervical length than with gestational age, and that it was somewhat higher in multiparous woman, particularly those with a history of preterm delivery [20].

The reliability of TDI-based cervical elastography for the quantitative assessment of cervical stiffness was assessed in our previous preliminary studies [6]. Natural strain was chosen because in subsequent studies the Lagrangian strain failed to perform in the 3rd trimester, when the cervixes are softer and the tissue deformation increases, while natural strain showed a high intra-operator reliability [7]. The current study, even if conducted by a single operator, confirms these results. Concerning the study of the clinical applicability of TS measurement, our results show a positive correlation between cervical TS and digital consistency assessment, supporting the usefulness of this new ultrasound tool for a quantitative evaluation of cervical stiffness. No correlation was shown between cervical TS and the two most relevant population features, gestational age and cervical length. Nonetheless, all included patients were at the end of pregnancy and it might be possible that elastography can provide more information when performed at different gestational ages.

In order to evaluate the predictability of labor induction success our study included only patients undergoing labor induction with vaginal progestin. This choice was made in order to reach better homogeneity of the results obtained with labor induction. Patients with PROM at admission were not included in the study, as membrane rupture can influence the process of cervical ripening and parturition. The cervical length was measured as the functional cervical length because of its better reliability and correlation with pregnancy outcome [21, 22]. The cervical length cut-off of 15 mm was subjective and introduced in order to permit an optimal process of strain calculation. Indeed, the cervix should at least fit the vaginal probe dimension, because the compression force should be exerted perpendicular to its longitudinal axis and lateral and longitudinal dislocation of the probe should be avoided. Otherwise, the reliability of the results...
would not be guaranteed, and the practicability of the tool would be limited.

The choice of different end points in our study reflects the uncertainty in the definition of adequate parameters for defining successful labor induction. Indeed, many confounding factors limit the homogenous interpretation of the abundant results present in the current literature: the heterogeneity of the considered population (for example, parity, gestational age and presence of PROM), but also the heterogeneity of the protocol used for labor induction (drug type, formulation and dosage applied, use of amniotomy or oxytocin for labor induction) and the evaluated outcome measures [23, 26]. In our opinion, active labor should be considered the most appropriate parameter to define successful labor induction, as cervical ripening and uterine contractions are the first targets of labor induction. Thereafter, many other confounding factors can interfere with the process of childbirth, for example a cesarean section in the case of a not reassuring or pathologic fetal heart rate pattern, use of oxytocin or amniotomy for labor augmentation or the occurrence of spontaneous membrane rupture. Nonetheless, the two endpoints, vaginal delivery and the total milligrams of PG used for labor induction, have the benefit of eliminating the bias of a subjective definition of active labor. The definition of further sub-categories helped to differentiate between “responders” and “non-responders” (successful versus failed labor induction), as well as between “early” and “late” responders (time to active labor < or > 24 hours, time to delivery < or > 36 hours and PG < or > 6 mg).

Our results show a low cervical TS (stiffer cervical tissue) to be related to failure of labor induction. Also a longer, functional cervical length by ultrasound was related to failure of labor induction, even if the p-value was only near statistical significance. Failed induction was recorded only in four cases: three cases due to failed cervical ripening and regular uterine contraction, one due to failed cervical ripening unless regular uterine contractions were reached. In this case, a very stiff cervix was reported during the whole labor, supporting the decision to perform a secondary cesarean delivery for failed cervical ripening. Conversely, cervical TS did not predict the other outcome measures studied but seemed to be more accurate than digital cervical consistency assessment. Interestingly, among these patients both the Bishop score and the functional cervical length were shown to predict only an early response to labor induction (time to labor induction < 24 hours, time to delivery < 36 hours and PG usage < 6 mg). Otherwise, they also failed to find a significant correlation in the prediction of labor inductions requiring a longer time or higher PG administration. These results are in accordance with most of the literature, describing the Bishop score as a useful parameter for predicting labor induction mainly in patients with favorable pelvic scores [27]. With regard to cervical length and success of labor induction, the current literature demonstrates that cervical length did not accurately predict any outcome, neither a successful vaginal delivery nor successful cervical ripening. Nonetheless, a differentiation between functional and total cervical length as well as a differentiation between early and late response to induction have not been considered [23].
The differentiation into subcategories in our study could explain the results in the literature and help to define a more suitable outcome when studying the success of labor induction in the future. The only unpredictable outcome measure was the success of delivery (vaginal versus cesarean delivery). This is probably due to the great variation of factors influencing the process of delivery, making it an unsuitable outcome measure for prediction.

**Study limits**

Even if very intriguing, results concerning the predictability of labor induction failure by means of cervical TS should be interpreted with caution, most of all because of the small number of patients matching this group. Otherwise, gestational age is most likely the main factor associated with a successful induction of labor and all included patients were at the end of pregnancy. It might be possible that elastography performed at a different gestational age could provide more relevant information for predicting the successful induction of labor. Similarly, it is possible that already shortened cervixes might not obtain maximal advantage from this further diagnostic tool, and that only patients with a greater cervical length should be considered when predicting the successful induction of labor with cervical elastography. Further studies in this regard are warranted.

Another limitation of the proposed tool is the dependency of cervical strain on the applied force, as well as the possible unwanted lateral or longitudinal dislocation of the cervical tissue during the movement of cervix compression. However, TDI-based quantitative elastography, performed under standardized conditions for raw dataset acquisition, proved to be feasible and to have high reliability. A similar method for cervical stiffness evaluation was recently described, with the only difference being that the calculation occurred manually. The anteroposterior cervical diameter was measured before and after the application of pressure on the cervix using the transvaginal probe. The calculation of the index of compression, called the cervical consistency index (CCI), showed an excellent intra- and inter-observer correlation [28].

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