Value of cervical electrical impedance spectroscopy to predict spontaneous preterm delivery in asymptomatic women: the ECCLIPPx prospective cohort study

D. O. C. ANUMBA¹, V. STERN¹, J. T. HEALEY², S. DIXON³ and B. H. BROWN²

¹Academic Unit of Reproductive and Developmental Medicine, Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK; ²Medical Physics and Clinical Engineering, University of Sheffield, Sheffield, UK; ³School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

KEYWORDS: cervical length; electrical impedance spectroscopy; fetal fibronectin; pregnancy; preterm birth; screening

CONTRIBUTION

What are the novel findings of this work?
Existing tools for predicting spontaneous premature birth have limited clinical utility. The findings of this study show that cervical electrical impedance spectroscopy (EIS) can predict spontaneous preterm birth in asymptomatic women as a standalone test as well as improve current risk-assessment approaches.

What are the clinical implications of this work?
Cervical EIS assessment during pregnancy provides a novel preterm birth risk assessment modality that can be adopted into clinical practice. Further studies may enable its incorporation into risk-assessment algorithms and decision-support tools to drive interventions and enhance personalized care.

ABSTRACT

Objectives Preterm birth (PTB) accounts for two-thirds of deaths of structurally normal babies and is associated with substantial lifetime healthcare costs. Prevention of PTB remains limited by the modest accuracy of prediction methods, namely transvaginal ultrasound (TVS) cervical length (CL) measurement and quantitative cervicovaginal fetal fibronectin (FFN) estimation. We report the first substantive study detailing the predictive performance of a cervical probe device based on electrical impedance spectroscopy (EIS) for PTB – the EleCtriCaL Impedance Prediction of Preterm birth by spectroscopy of the cervix (ECCLIPPx) study. We aimed to compare the accuracy of cervical EIS-based prediction of spontaneous PTB with that of prediction using TVS-CL and FFN in asymptomatic women in the mid-trimester.

Methods We studied asymptomatic women with a singleton pregnancy at 20–22 weeks' and 26–28 weeks' gestation. EIS was performed using a Sheffield Mark 5.0 device that makes measurements in the frequency range 76 Hz to 625 kHz using a small probe housing tetrapolar electrodes. TVS-CL and FFN were also measured. The associations of cervical EIS, TVS-CL and FFN with spontaneous delivery before 37 weeks and before 32 weeks were determined by multivariate linear and non-linear logistic regression analysis. Areas under the receiver-operating-characteristics curves (AUC) plots of sensitivity against specificity were used to compare the predictive performance of all parameters, both in isolation and in combination.

Results Of the 365 asymptomatic women studied at 20–22 weeks who were not receiving treatment, 29 had spontaneous PTB, 14 had indicated PTB and 322 had term birth. At the higher frequencies assessed, cervical EIS predicted spontaneous PTB before 37 weeks with an AUC of 0.76 (95% CI, 0.71–0.81), compared with AUCs of 0.72 (95% CI, 0.66–0.76) for TVS-CL and 0.62 (95% CI, 0.56–0.72) for FFN. Combining all three assessments improved the prediction of spontaneous PTB before 37 weeks (AUC, 0.79 (95% CI, 0.74–0.83)) compared with TVS-CL and FFN alone. Incorporating a history of spontaneous PTB (defined as previous mid-trimester miscarriage or spontaneous PTB (14 to < 37 weeks)) into the cervical EIS prediction model improved the accuracy of cervical EIS-based prediction of spontaneous PTB.

© 2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.
of prediction of spontaneous PTB before 37 weeks (AUC, 0.83 (95% CI, 0.78–0.87)) and before 32 weeks (AUC, 0.86 (95% CI, 0.82–0.90)).

Conclusions Mid-trimester cervical EIS assessment predicts spontaneous PTB. Larger confirmatory studies investigating its potential clinical utility and to inform effective preventive interventions are required. © 2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Preterm birth (PTB) affects 15 million babies (6–18% of live births) annually. Early (before 28 weeks’ gestation) and late preterm babies suffer neurocognitive deficits, respectively, with some developing chronic diseases. Although the survival rate following PTB has improved, the incidence of PTB has plateaued or risen. Prevention of PTB remains limited by a lack of accurate predictive tests and therapies.

The current mainstay of PTB risk assessment is transvaginal ultrasound (TVS) measurement of cervical length (CL) and determination of cervicovaginal fluid fetal fibronectin (FFN). Although both techniques have modest predictive value in high-risk asymptomatic women, their sensitivity is low in low-risk populations. While findings are variable, most reports suggest that the majority of women with a short cervix (<15 mm) will not deliver before 32 weeks, limiting the utility of CL measurement for the prevention of spontaneous PTB, particularly among nulliparous women with a singleton pregnancy. The cost-effectiveness of CL and FFN assessment is also unclear.

The effectiveness of interventions based on CL-determined risk of PTB remains controversial; progesterone treatment for women with a history of PTB or a short cervix on ultrasound has established limited efficacy for prolonging gestation and, based on some studies, for preventing adverse neurodevelopmental and other health outcomes. Given that the syndrome of PTB has multiple etiologies, novel risk assessment modalities may improve stratification of patients and enhance the effectiveness of existing and new preventive interventions.

Assessing the cervical matricellular remodeling changes that precede birth is a logical target for PTB screening. Electrical impedance spectroscopy (EIS) non-invasively quantifies cervical tissue impedance to the passage of a small electrical current. Tissue impedance is influenced by several factors, including cell layering, the intra- and extracellular spaces, cell membrane capacitance and tissue hydration. There has been increasing application of EIS in screening for cervical and breast cancers.

Having demonstrated previously that EIS can detect prelabor cervical remodeling changes, and following the observation in a limited pilot study that mid-trimester cervical impedance in women at risk of PTB seemed to predict delivery before 37 weeks with an accuracy comparable to that of ultrasound-derived CL, we aimed to determine whether cervical EIS can predict spontaneous PTB, as compared to prediction using TVS-CL and/or FFN, in asymptomatic women in the mid-trimester.
Impedance spectroscopy to predict preterm birth

The measurement process was gated to ensure that the applied force was $2 \pm 0.2\, \text{N}$, which corresponds to a pressure of $21\, \text{kPa (157 mmHg)}$.

The device measures transfer impedance by applying current at 14 frequencies ranging from $76.3\, \text{Hz}$ to $625\, \text{kHz}$ in octave increments via an adjacent pair of injecting electrodes, and voltage is measured between the remaining pair of sensing electrodes. Each frequency sweep takes $200\, \text{ms}$ and, as a quality-control measure, these are repeated until the standard error (SE) of eight subsequent measurements is below a threshold. This yields a minimum time required to record the full-frequency spectrum of $1.6\, \text{s}$ and $3.2\, \text{s}$ for both electrode rings. The transfer impedance spectral measurements, together with their variance, is transmitted to the bespoke controlling PC application via Bluetooth technology and stored on a custom central database (ArQ; Scientific Computing, Sheffield Teaching Hospitals, Sheffield, UK).

Cervical EIS measurements are highly repeatable, as demonstrated by a mean (SE) coefficient of variation of impedance measurement of $7.3\, (1.1)\%$ in the frequency range $39.5–312.5\, \text{kHz}$, which was determined in our preliminary pilot study$^{44}$ to be potentially predictive of PTB. In this electrical frequency range, the mean intraclass correlation coefficient of variation of the Mark 5.0 device was predetermined to be $0.91\, (95\% \text{ CI}, 0.74–0.98)$.

Given that pregnancy is associated with changes in cervical epithelium that include ectropion formation and physiological high-grade metaplasia$^{50}$, we matched the EIS spectra to previously generated templates corresponding to normal squamous and columnar epithelia using a minimum least squares method$^{51}$. As described previously$^{51}$, these templates generated from three-dimensional finite element models of epithelial tissue types$^{52,53}$ have been shown to improve discrimination for clinical study outcomes in the cervix$^{51}$ and the tongue$^{38}$. Measured EIS spectra were used to construct probability distributions for each tissue type, enabling determination of the relative probability that the measurement corresponded to columnar or squamous epithelium.

**Experimental procedure**

All measurements were performed by a single operator after structured training on capturing EIS measurements and TVS measurement of CL, employing a standardized experimental protocol. On attendance, each woman had triple high vaginal swabs (sterile Dacron swabs; Deltalab Eurotubo 300 263, Fisher Scientific, Loughborough, UK) taken to obtain cervicovaginal fluid, after the passage of a sterile Cusco’s vaginal speculum, with one swab sample used to quantify FFN using the 10Q Rapid FFN analyzer (Hologic, Marlborough, MA, USA) and another sent for bacteriological assessment. The sterile electrical impedance probe was then introduced and gently touched on the anterior lip of the cervix, and a button was pressed to capture data automatically once a steady-state application pressure of $2\, \text{N}$ had been attained$^{48}$. Three consecutive measurements were taken in quick succession over about $2\, \text{min}$ from each subject. Following removal of the device and the speculum, a transvaginal scan was performed to measure CL, and the shortest of three measurements was recorded. All data obtained were captured automatically in the ArQ database software, which also subsequently captured participant details from clinical records. The operator was blind to the EIS data at the time of capture. Clinicians provided standard clinical care for the participants without knowledge of the EIS results. Ultrasound-indicated cerclage, vaginal progesterone and expectant care were offered for women with a short cervix ($<25\, \text{mm}$), taking into account...
previous pregnancy history, the current gestational age and the woman’s preferences.

**Study outcomes**

The primary prediction outcome of the study was spontaneous delivery before 37 weeks’ gestation. The secondary outcome was spontaneous delivery before 32 weeks.

**Sample-size estimations**

Sample-size estimations were based on data from our pilot study and Jessop Wing birth statistics. We estimated that, in order for EIS to be clinically useful, it should demonstrate reasonable sensitivity and specificity of over 80%. We reasoned that, if cervical EIS predicted PTB with a sensitivity of within ± 10% (i.e., 95% CI from 75 to 95%), we would require 49 women who delivered early to be included in our study population in order to have a sufficient subset of spontaneous PTB cases. Assuming that about 25% of women at high risk of PTB deliver before 37 weeks, as reported in the literature, to have a sufficient subset of spontaneous PTBs, we would need 4 x 49 (i.e., around 200) high-risk women (with a history of spontaneous PTB) to be included. This number would be sufficient for estimating specificity with a reasonable degree of precision, since there would be up to 150 high-risk women who did not deliver prematurely. The precision for the specificity estimate would therefore be within ± 0.06 points, i.e., 95% CI, 79–91%. To assess EIS performance in women with no history of spontaneous PTB, we also recruited 250 women with no risk factors for PTB, a population for which current predictive tests have limited value, yet which accounts for > 50% of PTBs.

**Statistical analysis**

Data analysis was carried out using SPSS 24 (IBM Corp., Armonk, NY, USA) and MedCalc 14.8.1 (MedCalc Software Ltd, Ostend, Belgium). The data are reported and presented according to the revised STAndards for the Reporting of Diagnostic accuracy studies (STARD) Statement. Descriptive statistics were employed to summarize all quantitative data. The normality of data was assessed using the Kolmogorov–Smirnov test. Categorical outcomes, such as spontaneous PTB before 32 weeks or before 37 weeks, were compared using the χ² test (or χ² test for trend in the case of ordinal outcomes). Continuous variables were compared using parametric (Student’s t-test) or non-parametric (Mann–Whitney U-test) tests, as appropriate.

Multivariate analysis, including multiple linear regression and multiple logistic regression, was employed to exclude subject and test variables that could influence and confound the results for the predictive performance of EIS for PTB. Following analysis of transfer impedance at the 14 studied frequencies, the top five frequencies that showed reduced transfer impedance magnitude in the spontaneous PTB group in this study (19.5–312.5 kHz) were used for further investigation using regression analysis. In addition to these inputs, the full spectra were also matched to templates for normal squamous and columnar tissues, as described previously, to give two additional model inputs. Given that a model performs optimally in the dataset employed to generate it, validation in another dataset from a similar population provides a better reflection of the usefulness of the model. We therefore employed these inputs, taken from a random subset (30% of all cases; n = 110) of the spectra measured from both the PTB group and term-delivery group, as a training set to produce a final set of model parameters – the EIS index (consisting of tissue transfer impedance values in the frequency range 19.5–312.5 kHz and template-matched probability estimates for normal squamous and columnar tissues) – which was then used prospectively on the remaining measured spectra (n = 255), to test the performance of the model in distinguishing between women with spontaneous PTB and those with term delivery. The output probability of spontaneous PTB was used to produce graphical receiver-operating-characteristics (ROC) curves of percentage sensitivity against 100 – percentage specificity, in order to determine the predictive accuracy of cervical EIS for spontaneous delivery before 37 weeks, quantified as sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and areas under the curves (AUC). Similar test-accuracy ROC curves were generated for TVS-CL and FFN. For further analysis, the probability of spontaneous PTB based upon the analysis of the cervical EIS spectra were combined with probabilities based upon CL and FFN, measured in the same women, to derive a ROC curve of the combined predictive probability of spontaneous PTB using the three modalities. Kaplan–Meier survival curves of time to delivery were produced to depict the predictive performance of EIS for spontaneous PTB based on an optimal cut-off value of the EIS index. Comparisons of test accuracy were also made for different sub-cohorts of pregnant women.

**RESULTS**

Of 449 pregnant women recruited, 365 were included in the study. Recruitment details, inclusion and exclusion characteristics and clinical outcomes are summarized in Figure 2. Eighty-four women were excluded from the analysis because of a history of colposcopic cervical treatment, progesterone therapy during the index pregnancy or indicated cervical cerclage for presumed cervical insufficiency. The 365 untreated women included 159 who were deemed to be at high risk for PTB based on a history of spontaneous PTB, while 206 women were deemed to be at low risk for PTB. In this untreated cohort, there were 29 spontaneous PTBs, 14 indicated PTBs and 322 term births (Figure 2). Participant demographic and clinical outcome characteristics are detailed in Table 1.
Smoking prevalence and maternal body mass index were significantly higher in women who delivered before 37 weeks than in those who delivered at term.

Cervical EIS measurements

Consistent with data obtained during an earlier feasibility study, readings obtained from the inner 3-mm tetrapolar electrode ring arrangement showed better separation of findings between the PTB and term-delivery groups and are reported here. In the cohort of women studied, cervical transfer impedance was significantly lower in women who delivered spontaneously preterm than in those who delivered at term when assessed in the frequency range 39.1–312.5 kHz (Table S1). In women at high risk for PTB who were studied at 26–28 weeks, cervical transfer impedance was significantly lower in the subset who delivered preterm when assessed in the frequency range 19.5–312.5 kHz (Table S2).

Model validation data for cervical EIS

The predictive performance of the developed model was similar in the training set and the validation/test set, as summarized in Table 2.

Predictive accuracy of cervical EIS at 20–22 and 26–28 weeks for spontaneous PTB

The combined total cohort of women was used to determine the overall predictive performance for spontaneous PTB of cervical EIS in comparison with TVS-CL and FFN (Figure 3). Cervical EIS, TVS-CL and FFN measured at 20–22 weeks were independently predictive of spontaneous PTB before 37 weeks. Combining all three modalities improved the prediction of spontaneous PTB before 37 weeks, as compared with TVS-CL ($P < 0.05$) or FFN ($P < 0.05$) alone (Figure 3a). Furthermore, cervical EIS showed higher predictive accuracy for spontaneous...
PTB than did TVS-CL in women with a short cervix (AUC, 0.83 vs 0.75 for CL < 15 mm (n = 16) and AUC, 0.84 vs 0.53 for CL 15–25 mm (n = 51)).

Cervical EIS, TVS-CL and FFN were also predictive of spontaneous delivery before 37 weeks in the subset of high-risk women who were studied again at 26–28 weeks (n = 121) (Figure 3b). In this subgroup, combining all three modalities improved the prediction of spontaneous

Table 1 Patient characteristics and birth outcomes in 365 asymptomatic pregnancies, according to preterm (< 37 weeks) or term (≥ 37 weeks) delivery

| Variable                  | Preterm delivery (n = 43) | Term delivery (n = 322) | P   |
|---------------------------|---------------------------|-------------------------|-----|
| Ethnicity                 |                           |                         |     |
| White                     | 36 (83.7)                 | 299 (92.9)              |     |
| Asian                     | 2 (4.7)                   | 8 (2.5)                 |     |
| Black                     | 5 (11.6)                  | 9 (2.8)                 |     |
| Arabic                    | 0 (0)                     | 2 (0.6)                 |     |
| Mixed                     | 0 (0)                     | 4 (1.2)                 |     |
| Age (years)               | 31 (28–36)                | 30 (26–33)              | 0.081|
| BMI (kg/m²)               | 29.4 (25.8–32.5)          | 24.6 (22.4–28.3)        | < 0.001|
| Parity                    |                           |                         |     |
| 0                         | 6 (14.0)                  | 132 (41.0)              |     |
| ≥ 1                       | 37 (86.0)                 | 190 (59.0)              |     |
| Prior PTD (24–37 weeks)   | 31 (72.1)                 | 101 (31.4)              | < 0.0001|
| Prior miscarriage (14 to 24 weeks) | 8 (18.6) | 40 (12.4) | 0.1271|
| CL (mm) at:               |                           |                         |     |
| 20–22 weeks               | 33 ± 9.8                  | 40 ± 6.7                | < 0.001|
| 26–28 weeks*              | 31 ± 8                    | 36 ± 7                  | 0.03  |
| FFN (ng/mL) at:           |                           |                         |     |
| 20–22 weeks               | 9 (4–52)                  | 6 (3–13)                | 0.010 |
| 26–28 weeks*              | 12.5 (4–67)               | 4 (2.8–12.5)            | 0.038 |
| GA at delivery (weeks)    | 36 (31–35)†               | 39 (39–40)              | < 0.001|
| Birth weight (g)          | 2340.5 (1747.3–2592.5)†   | 3435.0 (3100.0–3780.0)  | < 0.001|

Data are presented only for spontaneous preterm-delivery cases (n = 29). BMI, body mass index; CL, cervical length; FFN, fetal fibronectin; GA, gestational age; PTD, preterm delivery.

Table 2 Model development: accuracy of cervical electrical impedance spectroscopy for prediction of spontaneous preterm birth (PTB) < 37 weeks in the training and test/validation sets

| Variable                  | Training set (n = 110) | Test/validation set (n = 255) |
|---------------------------|------------------------|-------------------------------|
| Spontaneous PTB < 37 weeks| 10.9 (9.1)             | 19 (7.5)                      |
| AUC (95% CI)              | 0.80 (0.72–0.87)       | 0.77 (0.69–0.86)              |
| Sensitivity               | 80.0 (44.0–98.0)       | 73.0 (67.0–80.0)              |
| Specificity               | 85.3 (77.0–92.0)       | 84.0 (77.0–92.0)              |

Data are given as n (%), mean ± SD. *Fourteen women in the preterm-delivery group and 107 in the term-delivery group were assessed at 26–28 weeks. †Data presented only for spontaneous preterm-delivery cases (n = 29).

Figure 3 Receiver-operating-characteristics (ROC) curves depicting predictive accuracy of cervical electrical impedance spectroscopy (EIS) (- - -), transvaginal ultrasound cervical length (TVS-CL) (-----), and fetal fibronectin (FFN) (-----) for spontaneous preterm birth (PTB) < 37 weeks of gestation in 365 asymptomatic women assessed at 20–22 weeks (overall cohort) (a) and in subset of 121 high-risk women with history of mid-trimester miscarriage or spontaneous PTB assessed at 26–28 weeks (b). (a) For assessment at 20–22 weeks in the overall cohort, areas under the ROC curves (AUCs) were: EIS, 0.76 (95% CI, 0.71–0.81), P < 0.0001; TVS-CL, 0.72 (95% CI, 0.66–0.76), P < 0.0001; FFN, 0.62 (95% CI, 0.56–0.72), P = 0.05. Combining all three modalities (EIS + TVS-CL + FFN) (-----) demonstrated significantly better prediction of spontaneous PTB < 37 weeks (AUC, 0.79 (95% CI, 0.72–0.83)) than did TVS-CL (P < 0.05) or FFN (P < 0.05) alone. (b) For assessment at 26–28 weeks in the high-risk group, AUCs were: EIS, 0.80 (95% CI, 0.71–0.88), P < 0.0001; TVS-CL, 0.66 (95% CI, 0.57–0.74), P < 0.05; FFN, 0.66 (95% CI, 0.57–0.75), P = 0.37. Combining all three modalities (EIS + TVS-CL + FFN) demonstrated significantly better prediction of spontaneous PTB < 37 weeks (AUC, 0.79 (95% CI, 0.74–0.83), P < 0.0001) than did TVS-CL (P < 0.05) or FFN (P < 0.05) alone.
Impedance spectroscopy to predict preterm birth

PTB before 37 weeks, as compared with TVS-CL (P < 0.05) or FFN (P < 0.05) alone (Figure 3b).

When employing the optimal predictive cervical EIS index cut-off at 20–22 weeks of 0.118 in a binary classification to assess the rate of pregnancy continuation to 42 weeks, Kaplan–Meier survival analysis of time-to-delivery curves showed high predictive performance of cervical EIS (χ², 37.4922; df 1; P < 0.0001) (Figure 4).

Figure 4 Kaplan–Meier survival plot showing time-to-delivery curves for 365 women assessed at 20–22 weeks' gestation, employing a binary classification based on an optimal predictive electrical impedance spectroscopy (EIS) index cut-off value of 0.118 to assess pregnancy continuation rates to 42 weeks. ——, EIS index ≥ 0.118; – – – – , EIS index < 0.118. Predictive EIS index, P < 0.0001.

Influence of obstetric history on cervical EIS prediction of spontaneous PTB

When taking into account history of spontaneous PTB, the accuracy of prediction of spontaneous delivery before 37 weeks and before 32 weeks was significantly better for cervical EIS than for TVS-CL (P < 0.01 for both) and FFN (P < 0.05 for both), when assessed at 20–22 weeks (Table 3). Furthermore, the predictive accuracy of cervical EIS for spontaneous PTB was not improved further by the incorporation of TVS-CL and FFN.

Table 3 Influence of history of spontaneous preterm birth (PTB) on predictive accuracy of cervical electrical impedance spectroscopy (EIS), cervical length (CL) by transvaginal ultrasound and fetal fibronectin (FFN) for spontaneous PTB in 365 asymptomatic pregnancies at 20–22 weeks' gestation

| Outcome/parameter | AUC Value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | LR+ | LR– |
|-------------------|-----------|----------------|----------------|---------|---------|-----|-----|
| Spontaneous PTB < 37 weeks (n = 29) |           |                |                |         |         |     |     |
| Cervical          | 0.83      | < 0.0001       | 81.0           | 72.0     | 20.4    | 97.7 | 2.86 | 0.27 |
| EIS + history     | (0.78–0.87)|                | (60.6–93.4)    | (66.2–76.8) | (16.5–25.0) | (95.0–98.9) | (2.2–3.7) | (0.1–0.6) |
| CL + history      | 0.71      | < 0.001        | 62.1           | 74.8     | 18.2    | 95.6 | 2.47 | 0.51 |
| FFN + history     | (0.66–0.76)| < 0.0001      | (42.3–79.3)    | (69.7–79.5) | (13.6–23.8) | (93.2–97.2) | (1.8–3.5) | (0.3–0.8) |
| Cervical          | 0.81      | < 0.0001       | 79.3           | 66.3     | 17.6    | 97.2 | 2.35 | 0.31 |
| EIS + CL + FFN + history | (0.77–0.85) | < 0.0001 | (60.3–92.0) | (60.8–71.4) | (14.3–21.3) | (94.5–98.6) | (1.8–3.0) | (0.2–0.6) |
| Spontaneous PTB < 32 weeks (n = 13) |           |                |                |         |         |     |     |
| Cervical          | 0.86      | < 0.0001       | 75.0           | 90.9     | 17.6    | 99.3 | 8.25 | 0.28 |
| EIS + history     | (0.82–0.90)| < 0.0001      | (34.9–96.8)    | (87.1–93.9) | (11.2–26.8) | (97.7–99.8) | (4.8–14.1) | (0.08–0.9) |
| CL + history      | 0.78      | < 0.0001       | 53.9           | 89.5     | 15.9    | 98.1 | 5.12 | 0.52 |
| FFN + history     | (0.74–0.82)| < 0.0001      | (25.1–80.8)    | (85.8–92.5) | (9.5–25.4) | (96.7–99.0) | (2.8–9.2) | (0.3–0.9) |
| Cervical          | 0.81      | < 0.001        | 69.2           | 89.1     | 19.1    | 98.7 | 6.38 | 0.35 |
| EIS + CL + FFN + history | (0.76–0.85) | < 0.0001 | (38.6–90.9) | (85.4–92.2) | (12.9–27.5) | (97.2–99.5) | (4.0–10.2) | (0.2–0.8) |

Values in parentheses are 95% CIs. history, history of spontaneous PTB (defined as previous spontaneous PTB or mid-trimester miscarriage); LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

© 2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.
DISCUSSION

In this study, we detail, for the first time, cervical EIS measurements in the mid-trimester of pregnancy for the prediction of spontaneous PTB (before 37 weeks). In our cohort of asymptomatic pregnant women, we compared EIS to conventional clinical tests – TVS-CL measurement and vaginal FFN quantitation. We showed that cervical EIS has a strong predictive potential for subsequent PTB in this untreated cohort, with predictive accuracy comparable with, and in some clinical situations better than, that of TVS-CL and FFN estimation. Larger studies are required to determine whether EIS may prove to be of clinical utility in the prediction of PTB, either as a standalone test or in conjunction with current clinical tests, more so when combined with maternal demographics and a history of spontaneous PTB.

Our findings are in agreement with those of our limited feasibility study of women at high risk of PTB, which similarly showed lower cervical-tissue transfer impedance values in the mid-trimester in those destined to deliver preterm. How cervical remodeling changes influence this observation remains unclear. EIS assesses dielectric tissue properties, which are influenced by cell volume, intra- and extracellular conductivities, cell plasma membrane capacitance and the functional state of cellular gap junction proteins. Tissue-transfer impedance also decreases with increasing hydration and edema. Cervical EIS assesses these properties in the epithelium, as well as the subepithelial stroma. Determining the relative contribution of these tissue characteristics to the measured impedance is hampered by the limited information available regarding cervical histologic and microscopic changes during pregnancy. However, it can be speculated that cervical remodeling changes that occur several weeks/months before labor account for the lower tissue-transfer impedance values in women destined to deliver preterm. Recent studies by our group and others have also demonstrated vaginal dysbiosis (characterized by community state types deficient in Lactobacillus species) in women destined to deliver preterm, which may modulate cervical epithelial and stromal remodeling, leading to PTB.

We have shown that mid-trimester cervical EIS has predictive accuracy for spontaneous PTB that is equal to or better than that of TVS-CL or FFN. Incorporating a history of spontaneous PTB into the risk-assessment model improved the prediction of spontaneous PTB by all assessed modalities, with the highest accuracies being achieved by cervical EIS alone or when combined with TVS-CL and FFN. We have also shown that cervical EIS has higher predictive accuracy for spontaneous PTB than does TVS-CL for women with a shorter cervix in our limited cohorts. Larger studies will determine whether cervical EIS can improve PTB risk assessment in pregnant women with a short cervix (< 15 mm), given that fewer than 1 in 25 of them will deliver before 32 weeks’ gestation. Such studies will also clarify the predictive performance of cervical EIS for PTB in nulliparous and low-risk women.

In this initial report, we detail the predictive performance of cervical EIS solely in pregnant women receiving no treatment intervention for PTB in order to reduce potential confounding. A larger study will be required to determine the value of cervical EIS in directing or assessing such interventions and in women who have had cervical surgery, those who have a congenital uterine malformation and in multiple pregnancies, given the dearth of adequate PTB risk-assessment approaches for these groups.

The predictive performance of TVS-CL and FFN for PTB before 32 or 37 weeks’ gestation in asymptomatic women studied in the mid-trimester in our series is in agreement with that in other reports for unselected pregnant women as well as for those with a history of PTB. Further, our limited data also highlight that combining EIS with TVS-CL and FFN for risk assessment in asymptomatic nulliparous women may improve the prediction of PTB, and warrants further study in this group of women, who currently have limited options for PTB risk assessment. If these studies are coupled with effective interventions and demonstrate benefit, they may enable the generation of better predictive algorithms and decision-support tools for the management of PTB.

If our observations are confirmed by larger studies, clinical adoption of cervical EIS as a PTB risk-assessment tool may confer several advantages. It would provide a hand-held point-of-care test that would require limited additional training of frontline care practitioners in the maternity healthcare setting. Regardless of the varied etiologies of the PTB syndrome, the EIS device assesses cervical remodeling, which is the final common path to the onset of preterm labor. It could potentially be employed for risk assessment for the majority of pregnant women. It can be employed in obese women subject to possible technical difficulties of visualizing the cervix during a pelvic examination. Minimal training is required, and technical proficiency may be achieved after about 10 measurements by a medically trained person able to perform a pelvic examination. An operating manual and/or training video would suffice to deliver such training. As it is distinct from existing risk-assessment approaches, EIS could prove complementary to them.

This study has several limitations. The sample size was limited and precluded assessment of women who had had cervical loop excisional treatment, cervical cerclage or progesterone, as well as those with a multiple pregnancy. The study population was mainly Caucasian, and further studies of women of other ethnicities will be required to demonstrate generalizability of the findings. Since a single operator obtaining all study measurements ensured better reliability of the data, interobserver performance of the measurements was not assessed. However, we have reported previously high inter- and intraobserver repeatability and reproducibility of cervical EIS. The limited sample size also precluded assessing...
cervical EIS prediction of secondary outcomes such as neonatal morbidity. Larger, multicenter studies will be required to determine the potential value of cervical EIS for routine unselected screening during pregnancy, the effects of treatments on EIS measurements and the potential incorporation of EIS into assessment and treatment algorithms, as well as health economic and value-of-information analyses.

In conclusion, subject to confirmation in larger studies, our observations suggest potential clinical utility of cervical EIS for PTB risk assessment, either as a standalone test or in conjunction with existing modalities.

ACKNOWLEDGMENTS

This project was wholly funded by the Medical Research Council of the UK (MRC Reference: MR/J014788/1). We thank Professor Stephen Walters (Health Economics Decision Support Unit) and Drs Lucy Gelder and Kathleen Baxter of the University of Sheffield Statistical Services Unit for statistical advice and assistance. Project management for the study was provided by Dr Evy De Leenheer.

REFERENCES

1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261–269.
2. Mwaniki MK, Atieno M, Lwanje JW, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 2012; 379: 445–452.
3. Marlow N, Wolfe D, Bracewell MA, Samara M; EPCure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2008; 358: 9–19.
4. Huddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32–33 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2003; 85: F21–F28.
5. Parkison JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
6. Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
7. Heath VC, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length measurement for the study was provided by Dr Evy De Leenheer.
8. REFERENCES
9. 1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261–269.
10. Mwaniki MK, Atieno M, Lwanje JW, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 2012; 379: 445–452.
11. Marlow N, Wolfe D, Bracewell MA, Samara M; EPCure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2008; 358: 9–19.
12. Huddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32–33 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2003; 85: F21–F28.
13. Parkison JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
14. Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
15. Heath VC, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length measurement for the study was provided by Dr Evy De Leenheer.
16. REFERENCES
17. 1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261–269.
18. Mwaniki MK, Atieno M, Lwanje JW, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 2012; 379: 445–452.
19. Marlow N, Wolfe D, Bracewell MA, Samara M; EPCure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2008; 358: 9–19.
20. Huddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32–33 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2003; 85: F21–F28.
21. Parkison JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
22. Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
23. Heath VC, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length measurement for the study was provided by Dr Evy De Leenheer.
24. REFERENCES
25. 1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261–269.
26. Mwaniki MK, Atieno M, Lwanje JW, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 2012; 379: 445–452.
27. Marlow N, Wolfe D, Bracewell MA, Samara M; EPCure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2008; 358: 9–19.
28. Huddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32–33 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2003; 85: F21–F28.
29. Parkison JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
30. Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
31. Heath VC, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length measurement for the study was provided by Dr Evy De Leenheer.
32. REFERENCES
33. 1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261–269.
34. Mwaniki MK, Atieno M, Lwanje JW, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 2012; 379: 445–452.
35. Marlow N, Wolfe D, Bracewell MA, Samara M; EPCure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2008; 358: 9–19.
36. Huddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32–33 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2003; 85: F21–F28.
37. Parkison JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
38. Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the value-of-information analyses. "Impedance spectroscopy to predict preterm birth. " 301
39. Heath VC, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length measurement for the study was provided by Dr Evy De Leenheer.
SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Cervical transfer impedance values measured at 20–22 weeks' gestation at 14 different frequencies in 351 asymptomatic women, according to spontaneous preterm (<37 weeks) or term (≥37 weeks) delivery

Table S2 Cervical transfer impedance values measured at 26–28 weeks' gestation at 14 different frequencies in 121 asymptomatic high-risk women, according to spontaneous preterm (<37 weeks) or term (≥37 weeks) delivery