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Raised electrical uterine activity and shortened cervical length could predict preterm delivery in a low-risk population

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Abstract

Purpose: To compare diagnostic accuracy of cervical length (CL) measurement and uterine electromyographic (EMG) activity in the second trimester regarding the prediction of preterm delivery (PTD).

Methods: Prospective study of 308 low-risk women. Shortened CL was defined as ≤ 25 mm (≤ 5th centile), while raised EMG activity was defined as presence of ≥ 20 action potentials in 20 minutes of assessment (≥ 95th centile). Outcome measures were diagnostic accuracy of both tests for prediction of PTD and early PTD (≤ 34 weeks).

Results: The incidence of PTD was 23/308 (7.4%) while the incidence of early was 9/308 (2.9%). Shortened CL and raised EMG activity are significantly related to PTD (prevalence-weighted likelihood ratio (pwLR) 1.9 (95%CI 1.0–3.5) versus 9.5 (95%CI 2.5–35.7), but not to early PTD (pwLR 0.4 (95%CI 0.2–0.8) versus 0.6 (95%CI 0.3-1.7). Significant predictive value for early PTD was found only if shortened CL was concomitant with raised EMG activity (pwLR 4 (95% CI 1.3-14.3).

Conclusion: Shortened CL and raised EMG activity in the second trimester have significant accuracy regarding the prediction of PTD in a low-risk population. However, in order to be useful as a predictor for early PTD, both tests must be positive.

Key words: *cervical length, low-risk population, second trimester, preterm delivery transvaginal ultrasound, uterine electromyographic activity.*

Introduction

Preterm delivery (PTD) and its consequences are leading cause of perinatal morbidity and mortality [1,2] . Nowadays there is an increasing attention in two topics related to screening for PTD; uterine electrical activity evaluated by electromyography (EMG) and cervical shortening assessed by sonographic cervical length (CL) measurement [3-9].

The uterine electrical activity has been revisited, particularly after development of a new, noninvasive transabdominal method of evaluation, and improved filtering systems which reduce recording artifacts [3,7-10]. When electrical activity involves many myometrial cells in immediate succession it produces action potentials [11,12]. A raised number of action potentials precede subsequent uterine contractions, and may be followed by cervical shortening and dilatation [9,12,13]. In our earlier investigation we found positive correlation between increased electrical activity of the uterine body and shortening of the CL [3]. Additionally, several investigators have reported the relation and usefulness of second trimester sonographic assessment of the CL for prediction of PTD in asymptomatic low-risk population [5,14-17].

Therefore, in this prospective study we compared for the first time the diagnostic accuracy of CL measurements and raised uterine EMG activity in the second trimester, separately and combined, for predicting PTD with particular attention to early PTD $\leq$ 34 weeks, in asymptomatic low-risk population of pregnant women.

Material and methods

This prospective cohort study was a part of a research project designed to assess the efficacy of different diagnostic methods used as a potential screening tests for PTD, and the study was performed between October 01 2007 and December 31 2009.

Entry criteria were: asymptomatic, low-risk nulliparous women with uncomplicated singleton pregnancy, booked for hospital care in the University Department of Obstetrics and Gynecology, Sveti Duh hospital, Zagreb, Croatia. The women were approached between 16 and 23 completed weeks of pregnancy when attending a routine hospital visit, and were enrolled after detailed explanation. Local (hospital) and University ethical committee approved the study protocol, and all participants in the study gave their informed written consent.

The predefined exclusion criteria were: clinically palpable uterine contractions; uterine pain or tenderness; temperature >38 C; white cell count above 14 x1012/l and/or C-reactive protein >15 mg/l; history of surgical procedures on the cervix (i.e. knife cone biopsy and loop electrosurgical excision); body mass index >25 kg/m2; developmental malformations of the Műllerian ducts found before pregnancy; cervical cerclage before enrolment; spasmolytic or tocolytic therapy; presence of other medical conditions that represent risk for preterm delivery (i.a. preeclampsia, autoimmune diseases, diabetes), and major congenital fetal anomalies or intrauterine fetal death.

Gestational age was determined by comparing a last menstrual period with ultrasound biometry performed in the first trimester. If the difference was found to be more than one week, ultrasound based gestational age was used for further calculations. The PTD was defined as delivery < 37 weeks whereas early PTD was defined as delivery $\leq$ 34 weeks.

Uterine EMG activity was assessed by a trained technician who was blinded to the results of sonographic CL measurement, using two bipolar surface Ag-Ag chloride disc electrodes (The 2-channel TECA™ Synergy T-EP System, Oxford Instruments, Oxon, UK). The electrodes were attached with adhesive tape symmetrically on both left and right sides of the abdominal projections of corneal part of the uterus and the reference electrode was placed on the woman's right wrist. Each assessment lasted for 20 minutes. The EMG activity was amplified, acquired and digitalized using TECA™ Synergy, EMG LivePlayTM software (Synergy T-EP system, Oxford Instruments, Oxon, UK). The data were filtered in the 0.1-4 Hz frequency range and the sampling frequency was set at 20 Hz. The raised EMG activity ($\geq 95^{th}$ centile for our population) was defined as presence of $\geq$ 20 action potentials with an amplitude at least 500 mV during the 20 minutes of evaluation. The picture of action potential is presented in Figure 1.

Transvaginal sonography was performed with a 7-MHz probe (model 6117, Aloka 5500, ALOKA CO. LTD, Tokyo, Japan), according to the previously described protocol by Owen et al [18]. The cervical assessment was carried out over a period of 3 - 5 minutes in order to detect spontaneous dynamic changes. At least three measurements were made and the lowest value was used for further calculations. The shortened CL was defined as length $\leq$ 25 mm ($\leq 5^{th}$ centile for our population).

The results obtained in the study were known to the principal investigators only, and pregnancy care was unaltered by participation in the study.

Statistical analysis

As a part of the study design, a sample size calculation was performed (Sample size calculator, MaCorr Inc., Toronto, Ontario, Canada). The calculation was designed to detect at least 10% difference between likelihood for prediction of early PTD between shortened CL and raised EMG activity. According to input criteria in we calculated that the confidence interval would be 5.9 %. Using a confidence level of 95% and confidence interval of 5.9 %, for our population the sample size needed to be 276 women.

Data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago IL, USA) and Vassar statistical package (http://faculty.vassar.edu/lowry/VassarStats.html). Raised EMG activity and shortened CL were the variables used to predict outcomes. The Kolmogorov–Smirnov test was used to determine whether the CL measurements were normally distributed. Centiles for the CL and number of action potentials were analyzed by the chi-squared test.

Outcome measures included sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% CI for shortened CL and raised EMG activity regarding the prediction of PTD and early PTD.

Additionally, among the various statistical measures that incorporate both sensitivity and specificity for description of validity of diagnostic or screening tests we opted for positive likelihood ratio (LR) and prevalence-weighted LR. In some circumstances, the prevalence-weighted LR gives different and better impression of the validity of a test especially in a population with a low prevalence for some outcomes. Therefore, conventional LR and prevalence-weighted LR weighted for positive results with 95 % CI were calculated comparing women with CL $\leq$5th centile with those >5th centile, and women with raised EMG activity $\geq$95th centile with those <95th centile.

Results

Totally, 369 women were approached for participation. We excluded 61 women (19 had clinically or biochemically suspected infection, 18 had body mass index >25 kg/m2, 12 were on some tocolytic or spasmolytic therapy, three had surgical procedure on the cervix, three had clinically palpable contractions two had cerclage before enrolment, and four refused to participate in the study). Final results were based on 308 pregnant women. Median maternal age at enrolment was 27 years (interquartile range 24-31) and median gestational age was 20 weeks (interquartile range 18-22). Mean CL was 38 mm with a standard deviation of 9 mm. Totally, 62/308 (20.1%) pregnant women had some EMG activity, with a median frequency of action potentials of 0.02 Hz (interquartile range 0.01-0.03) and a median amplitude of action potentials of 1000 mV (interquartile range 500-1500). Raised EMG activity ($\geq$ 95% centile for our population) had the highest predictive value regarding the prediction of PTD.

The incidence of PTD in our group was 23/308 (7.4%) while the incidence of early PTD weeks was 9/308 (2.9%). A shortened CL was found in 23/308 (7.4%) women. Of them seven delivered $\leq$34 weeks. Raised EMG activity was found in 21/308 (6.8%). Of these women eight delivered $\leq$34 weeks. Diagnostic accuracy of shortened CL and raised EMG activity is presented at Tables 1 and 2. Shortened CL and raised EMG activity alone predicted PTD with a prevalence-weighted LR of 1.9 (95%CI 1.1–3.5) for CL and 9.5 (95%CI 2.5–35.7) for EMG, but not early PTD (prevalence-weighted LR 0.4 (95% CI 0.2–1.8) for CL and 0.6 (95%CI 0.3-1.7) for EMG. However, prevalence-weighted LR was significant for a combination of the two tests combined, both for PTD (prevalence-

weighted LR 9, 95%CI 1.4-58.4) and early PTD (prevalence-weighted LR 4, 95%CI 1.3-14.3).

Discussion

Raised EMG activity and shortened CL have a significant diagnostic potential regarding prediction of PTD. Sonographic CL measurement and its shortening in the second trimester is one of the strongest predictors for PTD in low-risk population [5,14-17]. The "cut-off" value of 25 mm for CL is the commonest and widely used in majority of previous studies that investigated the relation of CL and incidence of PTD [5,14-16].

EMG activity together with cervical shortening is related to the initiation of PTD and term delivery as well. [6,7,19,20]. Abdominal uterine EMG assessment is a simple, noninvasive, easy and well accepted method for understanding uterine physiology [3,6-13]. Frequent action potentials precede increased uterine mechanical activity that could induce cervical shortening and potentially resulting in subsequent PTD [3, 9,12,13]. Normal electrical activity of the uterus throughout pregnancy consists of low amplitude EMG bursts [7]. Therefore, action potentials below 500 mV were considered to be normal.

Results of a recent study of Most et al. suggested that raised uterine EMG activity may help in identification of pregnant women in true rather than threatened PTD < 35 weeks [6]. They concluded that EMG uterine assessment and identification of pregnant women could be a useful parameter in prediction of PTD [6]. Maner et al. concluded that raised uterine EMG activity in the third trimester may predict delivery within 24 hours at term and within four days in PTD [7], whereas Verdenik et al. found that raised uterine EMG activity had sensitivity of 47% and specificity of 90% for prediction of PTD in the late second and third trimester of pregnancy [19].

Previously published reports of EMG uterine assessment as a screening test regarding for PTD were done after the 24th gestational week. Our study is the first that compare CL measurement and uterine EMG activity in early second trimester, the earliest gestational age where EMG is possible using transabdominal approach. This makes our results even more important, particularly as we previously found that raised uterine EMG activity is in positive correlation with shortened CL [3].

In conclusion the combination of two different pathways which includes increased uterine electrical activity and cervical shortening could become a new and valuable parameter regarding the prediction of PTD and early PTD in population of low-risk pregnant women.

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Table 1

Diagnostic accuracy of uterine EMG activity and cervical length regarding the prediction of PTD < 37 weeks

Variable	CL	EMG	CL + EMG
Cut off value (percentile)	≤25 mm (5^{th})	≥20 action potentials (95^{th})	≤25 mm + ≥20 action potentials
Positive test result (%, n)	7.4%, 23/308	6.8%, 21/308	3.2%, 10/308
Sensitivity (% [95% CI], n)	65.2%[45.1-85.3],15/23	82.6%[60.4-94.3],19/23	39.1%[20.5-61.1],9/23
Specificity (% [95%CI], n)	97.2%[94.3-98.7],278/285	99.3%[97.2-99.9],282/285	99.6%[97.7-99.9],284/285
PPV (% [95% CI], n)	65.2%[45.1-85.3],15/23	90.5%[68.2-98.3],19/21	90%[54.1- 99.5],9/10
NPV (% [95% CI, n)	97.5%[94.8-98.9],278/285	98.6 %[96.2-99.5],282/287	95.3%[92.1-97.3],284/298
LR+ c [95%CI]	24.4 [11.6-51.1]	117.3 [29.1-472.4]	111.5[14.8-842.2]
LR + wp [95%CI]	1.9[1.0-3.5]	9.5 [2.5-35.7]	9[1.4-58.4]

Abbreviations:

CL – cervical length, EMG – electromyography, N – number, CI – confidence interval, PPV – positive predictive value, NPV – negative predictive value, LR+ c – likelihood ratio for positive results conventional, LR + wp - likelihood ratio for positive results weighted by prevalence

Table 2

Diagnostic accuracy of uterine EMG activity and cervical length regarding the prediction of PTD ≤ 34 weeks

Variable	CL	EMG	CL + EMG
Cut off value (percentile)	≤ 25 mm (5^{th})	≥20 action potentials (95^{th})	≤ 25 mm + ≥20 action potentials
Positive test result (%, n)	7.4%, 23/308	6.8%, 21/308	3.2%, 10/308
Sensitivity (% [95% CI], n)	77.8%[40.1-96.2],7/9	88.8%[50.7-99.4],8/9	88.8%[50.7-99.4],8/9
Specificity (% [95%CI], n)	94.6%[91.3-96.8],283/299	95.6%[92.5-97.6], 286/299	99.3%[97.3-99.8],297/299
PPV (% [95% CI], n)	30.4%[14.1-53.2],7/23	38.1%[18.9-61.3],13/21	80 %[44.2- 96.4],8/10
NPV (% [95% CI, n)	99.3%[97.2-99.9],283/285	99.6 %[97.7-99.9], 286/287	99.7%[97.8-99.9],297/298
LR+ c [95%CI]	14.5 [8.1-26.2]	22.4 [11.4-36.5]	132.9 [32.7-539.1]
LR + wp [95%CI]	0.4 [0.2-1.8]	0.6 [0.3-1.7]	4 [1.3-14.3]

Abbreviations:

CL – cervical length, EMG – electromyography, N – number, CI – confidence interval, PPV – positive predictive value, NPV – negative predictive value, LR+ c – likelihood ratio for positive results conventional, LR + wp - likelihood ratio for positive results weighted by prevalence

Figure 1

The picture of EMG action potential