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# **Screening for preterm labor in low risk population using vaginal pH and ultrasound cervical length measurement in mid trimester**

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**Synopsis:** Elevated vaginal pH in comparison shortened cervical length in mid trimester has better diagnostic accuracy regarding the prediction of early preterm labor in low-risk population

## **Abstract**

**Objective:** To assess diagnostic accuracy of vaginal pH and cervical length (CL) measurement in mid trimester in order to predict preterm labor (PTL).

**Methods:** Prospective cohort study of 316 low-risk pregnant women. Vaginal pH was measured using test gloves for measuring the vaginal acidity, while CL was measured using transvaginal ultrasound. The cut off value for vaginal pH used was 5.0 (95<sup>th</sup> centile for our population) whereas shortened CL was defined as  $\leq 26$  mm (5<sup>th</sup> centile for our population).

**Results:** Elevated vaginal pH was found in 4.4% whereas shortened CL was found in 2.8%. The incidence of PTL (< 37 weeks) was 7.2%, and early PTL ( $\leq 34$  weeks) was 3.4%. Shortened CL is significantly related to PTL (LR weighted by prevalence 2.7, 95% CI 1.1–6.7) but is not to early PTL (LR weighted by prevalence 0.8, 95% CI 0.4–1.8). Elevated vaginal pH is better predictor of PTL (LR weighted by prevalence 3.7, 95% CI 1.3–10.4) and early PTL (LR weighted by prevalence 1.7, 95% CI 1.1–3.1).

**Conclusion:** Elevated vaginal pH has better accuracy in comparison with shortened CL regarding the prediction of early PTL in low risk pregnant women.

## **Introduction**

Despite intensive research and numerous advances achieved in modern perinatal medicine, preterm labor (PTL) still remains the leading contributor to perinatal mortality and morbidity <sup>1</sup>. In recent years there was increasing interest in two topics related to screening for PTL; bacterial vaginosis (BV) and cervical insufficiency. Both of them can be diagnosed using simple, safe, well accepted, reliable and reproducible methods; and they are potentially treatable <sup>1-3</sup>.

Bacterial vaginosis is commonest lower genital tract infection in women of reproductive age <sup>4</sup>. By definition, it is an imbalance of the vaginal ecosystem caused by overgrowing the normal lactobacilli flora by *Gardnerella vaginalis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Mobiluncus* species, *Prevotella* species and other anaerobes <sup>5-6</sup>. It is usually asymptomatic disease but associated with increased rate of PTL and unfavorable fetal outcome <sup>1,2,5,7-12</sup>. However, despite that BV is potentially treatable, recent meta-analysis shows conflicting data about the benefits and risks of routine screening for BV, especially in the low risk population <sup>3,5,13</sup>.

Similar things may apply for cervical insufficiency and its relation to PTL. It is also asymptomatic condition, it is approachable by simple diagnostic methods and potentially treatable <sup>1,2,14-17</sup>. Numerous investigators reported the relationship and usefulness of transvaginal ultrasound assessment of the uterine cervical length (CL) in mid trimester regarding the prediction of PTL in asymptomatic low-risk pregnancies. <sup>1,17-20</sup>.

In order to assess diagnostic potential for PTL screening in low risk population, we performed prospective cohort study of cervical insufficiency assessment by ultrasound measurement of CL and detection of BV by measuring vaginal pH in mid trimester.

## Materials and Methods

This prospective cohort study was a part of a research project designed to assess the efficacy of different diagnostic methods as a potential screening tests for PTL (Croatian Ministry of Science, Education and Sport, Project No 108-0000000-0378).

At University Department of Obstetrics and Gynecology, Medical School, "Sveti Duh" Hospital, Zagreb, Croatia; pregnant women with uncomplicated singleton pregnancy between 18 and 24 weeks were approached and offered participation in the study. At that gestational age all women are booked for anomaly scan and therefore attending our hospital clinic eliminating the need for additional hospital visit.

The exclusion criteria for enrollment were:

1. Positive history of previous PTL,
2. Pregnancy after method of assisted reproduction (IVF/ET),
3. Clinically (palpable uterine contractions, abdominal pain, and temperature  $> 38.5$  C) or laboratory (White cell count  $\geq 16 \times 10^{12}/l$ , C reactive protein  $\geq 10$  mg/l) suspected chorioamnionitis before enrollment,
4. Preterm prelabour rupture of the membranes or vaginal hemorrhage,
5. History of surgical procedure on the cervix (i.e. knife cone biopsy etc.),
6. Developmental malformations of Müllerian ducts found before pregnancy,
7. Cervical cerclage before enrollment,
8. The use of any local vaginal preparations that could influence on vaginal pH value in the last 24 hours or sexual intercourse in the last 24 hours,
9. Other medical conditions that are risk factors for preterm delivery (i.e. preeclampsia, auto immune diseases, diabetes etc.),
10. Major congenital fetal anomalies or intrauterine fetal death.

Gestational age was determined by comparing a last menstrual period (if available) with a corrections made on ultrasound measurements performed at first trimester scan. Because of conflicting results about potential benefits and/or harms of screening and treating asymptomatic women for BV and/or

cervical insufficiency, the results obtained in the study were known to the principal investigators only (RM, OG and MK), and the course of the pregnancy was unaltered by the participation in the study. Local and national ethic committee approved the study protocol and all women included in the study gave their informed written consent.

In order to assess BV the vaginal pH was measured using CarePlan VpH (Unipath Ltd, Bedford, MK33 3UP, UK) test gloves for measuring the vaginal acidity. The glove was used in the standard matter inserting the index finger with a test paper in posterior vaginal fornix. The lubricants were not used in order to avoid possible influence to the results. The vaginal pH 5.0 ( $> 95^{\text{th}}$  centile) for our study population was defined as elevated and used as predictive parameter for BV. The same cut off value has been used in many other studies<sup>11, 21-23</sup>.

Ultrasound examination of the cervix was performed immediately after the measurement vaginal pH with a 7-MHz transducer (model 6117, Aloka 5500, ALOKA CO. LTD, Tokyo, Japan). Every cervical screening was performed according to the protocol described by Owen et al<sup>14</sup>. The CL below the 5<sup>th</sup> centile was defined as shortened ( $\leq 26$  mm) and suggestive of cervical insufficiency. This value is in concordance to the previously published results for our population ranging from 25 do 26 mm<sup>18-20</sup>.

Every pregnant woman was scanned only once for study purposes by one of the investigators. The cervical assessment was carried out over a period of 3 - 5 minutes in order to detect spontaneous dynamic cervical changes. At least three measurements were made and the lowest value was used for further calculations.

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 PTL  $\leq 34$  weeks between shortened CL and high vaginal pH in low risk population. As a first step the confidence interval (CI) was determined using the confidence level of 95% in a sample population of 100 participants with at least 10% difference in likelihood for prediction of PTL between two parameters. The program has calculated that CI is 5.9

%. As a second step using confidence level of 95% and CI of 5.9 % the program has calculated that for our population the sample size needs to be 276 subjects.

Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago IL, USA). Vaginal pH value and CL were the variables used to predict outcomes. Centiles for the CL and vaginal pH were analyzed by the use of chi-square tests. For vaginal pH the cut off value  $\geq$  95th centile ( $\geq$  5.0) for our population was defined as elevated. Cervical length  $<$  5th centile ( $\leq$  26 mm) was defined as shortened.

Outcome measures included sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% CI for shortened CL and elevated vaginal pH regarding the prediction of PTL  $<$  37 weeks and early PTL  $\leq$  34 weeks.

Among 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 LR weighted by prevalence. Other classical statistical measures, including LR, are based exclusively on sensitivity and specificity and therefore they do not accept disease prevalence. In some circumstances, the accuracy weighted by prevalence gives different and better impression of the validity of a test especially in a population with a low prevalence for some outcomes.

We calculated conventional LR and LR weighted by prevalence for positive results with 95 % CI comparing subjects with CL  $\leq$  5<sup>th</sup> centile with those  $>$  5<sup>th</sup> centile, and subjects with vaginal pH  $\geq$  95<sup>th</sup> centile with those  $<$  95<sup>th</sup> centile.

## Results

During the study period (March 2007 to September 2009) 343 women were approached fulfilling predefined entry criteria; 23 decided not to participate and 4 were lost from follow up (i.e. did not deliver in our hospital neither were available by the phone number or address given at enrolment). Therefore, our final analysis was based on 316 women.

All of them had assessment of vaginal pH and transvaginal ultrasound examination of the cervix between 18 and 24 weeks gestation. Maternal age (median [interquartile range (IQR)]) at enrollment was 30 [27-35] years and median gestational age was 19 and IQR [18-22] weeks. Mean CL was 41 mm with standard deviation of 8, and the median vaginal pH value was 4.4; IQR [4.0-4.7].

The incidence of PTL < 37 weeks in our group was 23/316 (7.2%) while the incidence of early PTL  $\leq$  34 weeks was 8/316 (2.5%). The shortened CL ( $\leq$  26 mm being below 5<sup>th</sup> centile for our study population) was found in 15/316 (4.7%) women (ranged between 4 to 26 mm). Four of them delivered at term while other 11 delivered < 37 weeks. Among them 7 delivered  $\leq$  34 weeks. Normal CL, i.e. above 5<sup>th</sup> centile for study population, was found in 301 (95.2%) women; 289 of them delivered at term while 12 delivered < 37 weeks and one delivered  $\leq$  34 weeks.

High vaginal pH of 5.0 and above that represents 95<sup>th</sup> centile for our study population was found in 14/316 women (4.4%). In population with high vaginal pH, 3 women delivered at term, 11 delivered < 37 weeks and among them 7 delivered  $\leq$  34 weeks.

Diagnostic accuracy of CL and BV in relation to PTL and early PTL are presented in Table 1 and 2. Shortened CL is significantly related to PTL (LR 35.1, 95% CI 12.1 – 101.4). Vaginal pH  $\geq$  5.0 had higher LR for prediction of PTL risk (LR 46.7, 95% CI 14.0 – 155.7). Similar observation is noted if LR weighted for prevalence is used. Regarding the risk assessment for early PTL, the results are in favor of vaginal pH above 5.0 (LR 38.5, 95% CI 17.7 – 83.8). If we take a prevalence of PTL into the calculation of LR, only pH  $\geq$  5.0 had statistical significance regarding the prediction of PTL  $\geq$  34 weeks (LR 1.7, 95% CI 1.1 – 3.1).



## Discussion

We found significant correlation between raised vaginal pH value and shortened ultrasound CL measurement regarding the prediction of PTL in low risk population. The distribution of CL values obtained in our study was similar to the previously published reports<sup>14-18</sup>. Comparing the accuracy for prediction of early PTL, the 5<sup>th</sup> centile of CL ( $\leq 26$  mm) in our study and the 5<sup>th</sup> centile of CL ( $\leq 22$ mm) in the study of Iams et al; our results showed better PPV (46.6% versus 26%) and better sensitivity (87.5% versus 30%)<sup>15</sup>. It is our belief that such difference is results of relatively low number of women included in our study but it might be also influenced by the CL cut of point value used in order to diagnose cervical insufficiency. The results of diagnostic accuracy obtained in this study are even better compared to some our previously published reports<sup>18, 19</sup>. We believe that this difference represents our personal learning curve improvement in CL assessment and screening for PTL.

The accuracy of our results, regarding the prediction of PTL  $\leq 37$  weeks is comparable with the results of Taipale and Hiilesmaa and the minor differences also can be explained by the relatively low number of women included<sup>16</sup>. With significant difference found on conventional LR and LR weighted by prevalence calculation (35.1 and 2.7) we conclude that CL measurement has its place in the assessment of low risk pregnant women in population based PTL screening programs. This is already confirmed by some of our previously published reports<sup>18, 19</sup>. Unfortunately, this significance is not so good in the assessment of low risk population for early PTL. Conventional LR is statistically significant being 33.7 (95% CI 16.2 – 70.1) but LR weighted by prevalence is not being 0.8 (95% CI 0.4 – 1.8).

Therefore, additional test would be very welcome and we expanded our cervical insufficiency screening program with screening for BV. Among the different diagnostic test for detection of BV we opted for vaginal pH measurement because its simplicity as well as correlation between increased pH value and BV<sup>11,20-22</sup>. Some investigators pointed out that increased vaginal pH  $\geq 5.0$  is the strongest predictors among different clinical predictors regarding the detection of BV<sup>11,21-23</sup>. Jazayeri et al. in their prospective study pointed out that pregnant women with elevated vaginal pH  $\geq 5.0$  had

significantly higher incidence of PTD < 37 weeks (OR 9.6, 95% CI 2.0 - 45.5)<sup>21</sup>. Furthermore, Simhan et al. in series of 13917 pregnant women found vaginal pH > 5.0 in second trimester strongly associated with PTD < 32 weeks (OR 1.7 [1.1-2.6])<sup>11</sup>. The results of Cauci et al. suggest that combinations of vaginal biomarkers (vaginal pH > 5.0, increased sialidase and prolidase activities) are associated with clinically important risks of PTL if performed in the second trimester<sup>22</sup>. Hauth et al. pointed out that only vaginal pH  $\geq$  5.0 in early pregnancy is significantly connected with higher incidence of PTL in comparison with pH < 5.0<sup>23</sup>.

Leitich and Kiss recently updated a previously published meta-analysis where they evaluated BV and intermediate vaginal flora as risk factors for adverse pregnancy outcome<sup>3,24</sup>. Totally, 32 studies with 30,518 patients were assessed. Outcomes were preterm delivery, late miscarriage, maternal or neonatal infection and perinatal mortality. They found that BV more than doubles the risk of preterm delivery in asymptomatic pregnant women (OR 2.16, 95% CI 1.56-3.00) as well as in pregnant women with symptoms of preterm labor (OR 2.38, 95% CI 1.02-5.58)<sup>24</sup>.

When vaginal pH value of 5.0 and more (representing 95<sup>th</sup> centile for our population) is used in order to define BV, the number of screening positive women was 4.4% (14/316), LR weighted by prevalence for PTL was 3.7 (95% CI 1.3 – 10.4) and 1.7 for early PTL (95% CI 1.1 – 3.1). This pH cut of point is significant and may be relevant for screening purposes in low risk population especially for prediction of early PTL. Regarding that matter, our results are similar compared to other authors pointing vaginal pH as one of the most predictive parameter for prediction of PTL but only using a cut off pH value of 5.0 and more<sup>21-24</sup>.

Based on our results it can be concluded that both, CL measurements and vaginal pH assessment, representing screening tests for cervical insufficiency and BV are highly specific and accurate in the screening for PTL in low risk population. However, high vaginal pH assessment has better diagnostic accuracy in prediction and determination of the risk for early PTL  $\leq$  34 weeks.

As recently published, interventions to reduce the morbidity and mortality related to PTL can be either primary (directed to all women), secondary (aimed at eliminating or reducing existing risk), or tertiary (intended to improve outcomes for preterm infants)<sup>25</sup>. In this aspect, regionalized care,

corticosteroids, tocolytic agents and antibiotics have reduced perinatal morbidity and mortality; but the incidence of PTL is still increased<sup>25</sup>. Therefore, advances in primary and secondary care are needed and may be useful for the benefits of the both, mother and their infants. We strongly believe that, screening programs designed to define population at risk for PTL may come closely to that goal.

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