Original research

The rate of cervical length shortening in the management of vasa previa

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Running headline: Cervical length in the management of vasa previa

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Abstract

Objective - There is no consensus about the optimal surveillance strategy in women diagnosed with vasa previa. The aim of this study was to evaluate the role of rate of change in cervical length (CL) measurements in the management of singleton pregnancies diagnosed with vasa previa.

Methods - We performed a retrospective case control study of our databases for pregnancies diagnosed prenatally with vasa previa and followed-up with transvaginal ultrasound for CL and evaluated the impact of the changes in CL on the need for emergency caesarean delivery.

Results - The cohort included 29 singleton pregnancies diagnosed prenatally with vasa previa in the second trimester of pregnancy. There were 14 and 15 pregnancies delivered by elective and emergent caesarean delivery, respectively. The rate of CL shortening was significantly slower for women with elective compared to emergent caesarean delivery ((median (range)); 0.7 (0.1-2.0) versus 1.5 (0.25-3.0) mm/week, p=0.011). For each additional millimeter per week decrease in CL, the odds of emergent caesarean delivery increase by 6.5 (95% CI, 1.02-41.20). The receiver operating characteristic (ROC) curve for rate of CL shortening in the prediction of emergency caesarean delivery yielded an area under the ROC curve of 0.85 (95% CI, 0.69-0.99).

Conclusion - Our findings indicate an association between the rate of CL shortening and the risk of emergent caesarean delivery in pregnancies diagnosed

with vasa previa in the second trimester. Further multicentric studies are required to validate our data prospectively and in particular the role of serial CL measurements in determining the optimal delivery time for individual cases.

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Key words: Vasa previa, cervical length, caesarean delivery, prenatal diagnosis, ultrasound

Introduction

Vasa previa occurs when fetal vessels run through the membranes (vasa previa type I), to cross cervix, either to reach a velamentous cord insertion (VCI) or to connect the placenta with a succenturiate or accessory lobe (vasa previa type II). Being unprotected by a firm fibrous chorionic plate or Wharton's jelly of the umbilical cord, these vessels are liable to rupture either in active labor or at amniotomy to induce or augment early labor.[1-3] The classic presentation of undiagnosed vasa previa in labour is the presence of painless vaginal bleeding. Because the total fetal blood volume at term is around 80–100 ml/kg, the loss of what may appear as a relatively small amount of blood can have major implications for the fetus and be rapidly fatal.[4,5]

A recent systematic review has found that the incidence of vasa previa is 0.6 per 1000 pregnancies.[6] The ultimate goal of management of vasa previa diagnosed during the second trimester of gestation is to prolong pregnancy safely while avoiding potential complications related to rupture of membranes before or during labor. Delivery by caesarean delivery of women with confirmed vasa previa is intuitive and logical and not based on RCT.Recent national guidelines, expert reviews and decision analysis study on the management of vasa previa have recommended elective preterm caesarean delivery of all asymptomatic women presenting with vasa previa between 34-36 weeks of gestation.[2,3,7,8] This management strategy is empirical and based on not being able to predict the optimal timing of delivery for individual women.

Ultrasound measurements of the cervical length (CL) has been shown to be useful in predicting and managing women at risk for preterm delivery,[9-12] as well as predicting the risk for emergency caesarean delivery in placenta previa .[13,14] Various definitions of short CL have been proposed A CL<25 mm, which corresponds to the 10th centile for CL in the general population[15] has been widely accepted as a threshold for abnormal CL at 23 weeks of gestation. Identifying short CL by ultrasound improves ability to predict preterm birth in individual cases, however, the rate of false-positive results remains high and most women with a CL<25 mm will deliver at term.[15] Recent cohort studies on the role of serial CL measurements in predicting preterm delivery have highlighted that the rate of cervical change is more accurate than a single CL measurements at a given moment in the second trimester.[16,17] Moroz and Simhan,[10] have also shown that in women with an initial short CL measurement of <25mm, the odds of preterm birth increased by 3% for each 1 mm of cervical shortening between ultrasound examinations. These findings support the concept that the process leading to preterm parturition is an active, ongoing phenomenon.

The aim of this study was to assess whether the rate of cervical length shortening is accurate in predicting the need for preterm emergency caesarean delivery in singleton pregnancies diagnosed prenatally with vasa previa and if serial CL measurements can play a role in the conservative managing of individual singleton pregnancies diagnosed with vasa previa during the second trimester of pregnancy.

Methods

We searched our databases for women with singleton pregnancies diagnosed with vasa previa during the second trimester of pregnancy between April 2005 and August 2016 who were followed-up with transvaginal ultrasound (TVS) for CL measurements. Our departments are using similar protocols based on international guidelines for the prenatal diagnosis of vasa previa i.e. demonstration with TVS of flow and fetal vascular waveforms on pulsed Doppler through at least 1 aberrant vessel within 2 cm from the internal cervical os.[3] The protocol for CL surveillance was implemented from the beginning of the study collection period. Exclusion criteria were singleton pregnancies with no CL follow-up measurements, pregnancies presenting with major fetal anomalies, multiple gestation, including twin pregnancies complicated by a vanishing twin or singleton pregnancies following selective termination to singleton pregnancies. The study was approved by the Institutional Review Boards in January 2017 (number 238-16).

CL was obtained as previously described.[18,19] In brief, for each TVS examination we obtained a sagittal view of the cervix and of the endocervical mucosa marking the cervical canal. The distance between the triangular area of echogenicity at the caudal tip close to the posterior wall of the upper vagina (the external os) and the “V” or the “U”-shaped notch at the end of endocervical mucosa (the internal os) was measured.[20] Both the external and internal ostium were identified at the two sides of the echogenic line. The distance from the surface of the posterior lip to the cervical canal was equal to the distance from the surface of the anterior lip to the cervical canal. Care was taken to avoid pressure on the

cervix as evidenced by the absence of increase echogenicity in the cervix. The closed preserved portion of the cervical canal was measured, and if cervical funneling was present, the remaining closed cervical length below the funnel was recorded. All women were asked to void their bladder before the examination and CL was measured three times without fundal pressure. The shortest measurement was then recorded. All measurements were performed by experienced sonographers with using TVS probes (5–9MHz frequency).

We follow asymptomatic women presenting with vasa previa with transvaginal ultrasound for vasa previa position and CL every 1-2 weeks from the time of the first diagnosis of vasa previa until delivery. The timing of the subsequent CL examination is based on the initial CL and the changes in CL between examinations. The timing for delivery is scheduled according to changes in CL and/or clinical symptoms (mainly uterine contractions, ruptured membranes and/or vaginal bleeding), following a course of corticosteroids. When the CL remains stable with normal fetal development and no clinical symptoms elective caesarean delivery is planned at 35-37 weeks. The prenatal diagnosis of vasa previa was confirmed in each case by postpartum examination of the placenta and membranes.

Statistical analysis

For the purpose if the analysis we separated the women into two groups according to their mode of cesarean delivery i.e. elective versus emergent caesarean delivery. Data on obstetrical history, mode of conception, gestational age and CL at diagnosis or last CL measurement between the two groups were compared.

The rate of cervical length shortening was calculated by dividing the difference between the initial CL measurement (mm) at the diagnosis of vasa previa and last CL assessment by the number of weeks between measurements (CL at diagnosis − last CL measurement)/ number of weeks between measurements). The data are reported as units of change in mm/week. Rounding was used in establishing gestational weeks or CL when calculating the rate of change and up to 6 days was considered a previous week of gestation. The rate of cervical length shortening was included as a dichotomous variable (cut-off point 0.7).

Descriptive variables are presented as mean and SD or as mean (range). Frequencies were presented as percentages. We used the Student's *t*-test for continuous variables and the Fisher's exact test for categorical data to compare the selected variables between the 2 studied groups. Two tailed p value of <0.05 was considered statistically significant.

Logistic regression analysis was used to determine which variable associated with emergent caesarean delivery in pregnancies with vasa previa. Odds ratios (OR) are given, including the 95% confidence intervals (CI). The receiver operating characteristic (ROC) curve was plotted. Calculations were performed in the statistical laboratory at Tel Aviv University using SPSS software (SPSS Inc., version 24 Chicago, IL, USA).

Results

159 The search of our databases identified 29 singleton pregnancies diagnosed
160 prenatally with vasa previa followed-up using our standard ultrasound protocol and
161 confirmed clinically at delivery. The patients were classified into two groups
162 according to mode of cesarean delivery. The first group included 14 women
163 delivered by elective caesarean delivery, and the second group included 15
164 women who underwent emergency caesarean delivery. Among the second group,
165 delivery timing was clinically indicated in 7 cases due to painful contractions or
166 active labor, in 3 cases due to premature rupture of the membranes, in 4 cases
167 due to vaginal bleeding in 4 (including two with ruptured membranes and a non-
168 reassuring fetal heart rate trace) and due to asymptomatic cervical shortening in
169 one case. Table 1 presents and compares the clinical data of the elective and
170 emergent groups.

171 There were no differences in gravidity, parity, previous caesarean delivery
172 and previous preterm delivery or mode of conception between the two study
173 groups (p>0.05, Table 1). Women delivered by elective caesarean delivery were
174 significantly older compared to those who had an emergency caesarean delivery
175 (years; mean±SD; 36.6±6.9 versus 31.7±2.9 years, p=0.02). The rate of CL
176 shortening was significantly slower for women with elective compared to emergent
177 caesarean delivery (median (range); 0.7 (0.1-2.0) versus 1.5 (0.25-3.0) mm/week,
178 p=0.011). The gestational age at delivery was significantly higher for women with
179 elective compared to emergent caesarean delivery (weeks; mean±SD; 36.8±1.2
180 versus 35.6±0.9 years, p=0.005). There was no significant (p>0.05,) difference in
181 CL at diagnosis or last CL assessment between the two groups.

Using a logistic regression analysis (univariable analysis), we found that the rate of CL shortening was significantly associated with the risk for emergent caesarean delivery. For every 1 mm/week decrease in CL, the odds of emergent caesarean delivery increase by 6.5 (95% CI, 1.02-41.20; p=0.027). The ROC curve for the rate of change in cervical length CL in the prediction of emergency caesarean delivery in pregnancies with vasa previa yielded an area under the ROC curve of 0.85 (95% CI, 0.69-0.99; Figure 1).

The cut-off point for the rate of CL shortening for the identification of women at high risk for emergency caesarean section as determined from the ROC curve (Figure 1) was>0.7 mm/week (with 86.7% sensitivity, 53.8% specificity, 68.4% positive predictive value (PPV) and 77.8% negative predictive value (NPV) (*P* = 0.04). In particular, women whose rate of CL shortening was >0.7 mm/week had a 7 times higher risk of emergent caesarean delivery (OR, 7.58 (95% CI, 1.19–48.0)).

Discussion

This is a first study evaluating the role of CL in singleton pregnancies presenting with vasa previa. The data of this study indicates that women diagnosed with vasa previa are more likely to require an emergent caesarean delivery if their cervix shortens rapidly on ultrasound examination and suggest that serial CL can contribute to the management of vasa previa and in particular to the timing of delivery of individual cases.

Transvaginal sonography is increasingly use to measure the CL in pregnancies at high risks of premature deliveries such as multiple pregnancies, placenta praevia or women with prior preterm birth. In women presenting with placenta previa, a shorter CL combined with increased thickness of the lower placental edge are predictor of antepartum bleeding and the need for emergent preterm caesarean delivery.[14,21] It has also been used to evaluate the risk of massive hemorrhage at delivery in women presenting with placenta previa.[22,23] On TVS at 28-33 weeks, the best CL cutoff for the identification of women at high risk of emergency caesarean delivery is ≤31 mm (16 times higher risk of preterm caesarean with 83.3% sensitivity, 76.6% sensitivity).[13] Using a similar CL cutoff, others authors found that women presenting with placenta previa with CL ≤30 mm in three studies (24-26) and ≤25 mm in two studies[24,25] had higher rates of antepartum bleeding requiring emergency delivery. In our series, we found that the rate of CL shortening for the identification of women at high risk for emergency caesarean section was >0.7 mm/week (with 86.7% sensitivity, 53.8% specificity, 68.4% PPV and 77.8% NPV). In particular, women whose rate of CL shortening was >0.7 mm/week had a 7 times higher risk of emergent caesarean delivery (OR, 7.58; 95% CI, 1.19–48.0). We also found that for each additional millimeter decrease in CL per week, the OR of emergent caesarean delivery increases by 6.5.

Iams has recently suggested that it is time to incorporate CL with a corresponding measure of time rather assessing static measurements at a given moment to study the preterm parturition process .[16] The value of transvaginal

ultrasound relies mainly on its high negative predictive value, varying from 76% for <20 mm to 100% for a threshold of <30 mm (38-42). However, the positive predictive value is low in identifying women who will deliver prematurely. For a CL of <25 mm, the positive predictive value is 15–31%.[15,30,31] Our findings are consistent with recent data highlighted the potential role to the rate of cervical change as a valuable tool for monitoring patients at risk and predicting preterm birth.[10,17,27] Additional studies support changes in understanding "threatened preterm labor" less as a distinct event than as a process that can occur over weeks or months at variable rates of cervical change.[10,32]

There is no consensus on the optimal surveillance strategy in women diagnosed with vasa previa. Data from a decision analysis study comparing 11 strategies for delivery timing in a patient with vasa previa found that an elective caesarean delivery between 34 and 36 weeks balances the risk of premature rupture of the membranes and subsequent fetal hemorrhage and death versus the risks of prematurity.[8] Antenatal hospitalization to allow for closer surveillance for signs of labor in a unit with appropriate neonatal facilities has also been proposed for all pregnancies presenting with vasa previa from 30-32 weeks of gestation,[2,33] but the evidence is weak and based on low-quality evidence.[3] Gibson *et al*. [34] reported the use of CL and fetal fibronectin status in the management of a pregnant women presenting with vasa previa on antenatal ultrasound.[34] It has also been reported that, in selected asymptomatic patients with vasa previa, there may be a role for outpatient management, especially if there is no evidence of cervical

shortening on transvaginal US and there are no symptoms of bleeding or preterm uterine activity.[35]

There are several limitations to the present study. Firstly, this is a retrospective review, which precludes control for additional factors associated with emergent caesarean delivery. Secondly, is the small number of cases available for analysis. This may influence the results by either introducing selection bias and/or restricting the statistical significance of the analysis. Furthermore, in a small number of cases, we were unable to calculate the average rate of change of CL from week to week between both groups and thus in those cases we could not evaluate whether the changes were gradual over time, early in the screening, or late in the screening process. However, we were able to identify a possible association between the rate of CL shortening with emergent caesarean delivery in patient with vasa previa and provide additional information on these subjects.

Approximately 90% of women with vasa praevia have also a velamentous cord insertion and 3-4% of women with a velamentous cords have vasa praevia.[1,2] Velamentous cords and vasa previa are much more common in twins than in singleton,[36] in pregnancies resulting from IVF,[37,38] bilobated and succenturiate placenta[39] and in low-lying and previa placenta.[2,7] The performance of ultrasound in diagnosing vasa praevia at the time of the mid-second trimester anomaly scan is considered excellent and TVS Color Doppler imaging ultrasonography provides the best diagnostic accuracy.[2,7] Our data suggest that consecutive targeted CL scanning of women with vasa praevia combined with its rate of shortening can assist clinicians in identifying those who are at risk for emergent caesarean

delivery. In view of the low prevalence of vasa praevia in the general population it is now necessary to evaluate the use of CL in its management in a larger multicentric study.

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425 **Table 1** Comparison of clinical data between women who underwent elective

426 caesarean delivery to those underwent emergency cesarean delivery by t-test.

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	Elective (n=14)	**Emergent (n=15)**	**P value**
Maternal age (years; mean ± SD)	36.6±6.9	31.7±2.9	**0.02**
Mode of conception (%)			
Spontaneous	40.0	60.0	0.466
Assisted reproductive technologies	57.1	42.9	
Obstetric history			
Gravidity (mean ± SD)	2.2±0.8	2.2±1.1	0.968
Parity (mean ± SD)	0.7±0.8	0.7±0.7	0.870
Previous Caesarean delivery (number (%))	3 (60.0)	2 (40.0)	0.651
Previous preterm delivery (number (%))	2 (33.3)	4 (66.7)	0.651
Current pregnancy			
Gestational age at diagnosis (weeks; mean (range))	24.5 (16-35)	26.1 (18-34)	0.481
Gestational age at delivery (weeks; mean ± SD)	36.8±1.2	35.6±0.9	**0.005**
Number of cervical length scans performed (mean ± SD)	3.5±1.5	3.4±1.1	0.83
TVCL measurement at diagnosis (mm; median (range))	39 (33-48)	38 (32-44)	0.225
Gestational age at last TVCL measurement (weeks; median (range))	35.5 (15-48)	30 (14-42)	0.796
Last TVCL measurement (mm; median (range))	34 (10-34)	29 (5-33)	0.060
Rate of cervical length shortening (mm/week; median (range))	0.7(0.1-2.0)	1.5 (0.25-3.0)	**0.011**

429 TVCL-transvaginal cervical length;

430 Data is presented as number (%) or as mean ± standard deviation.

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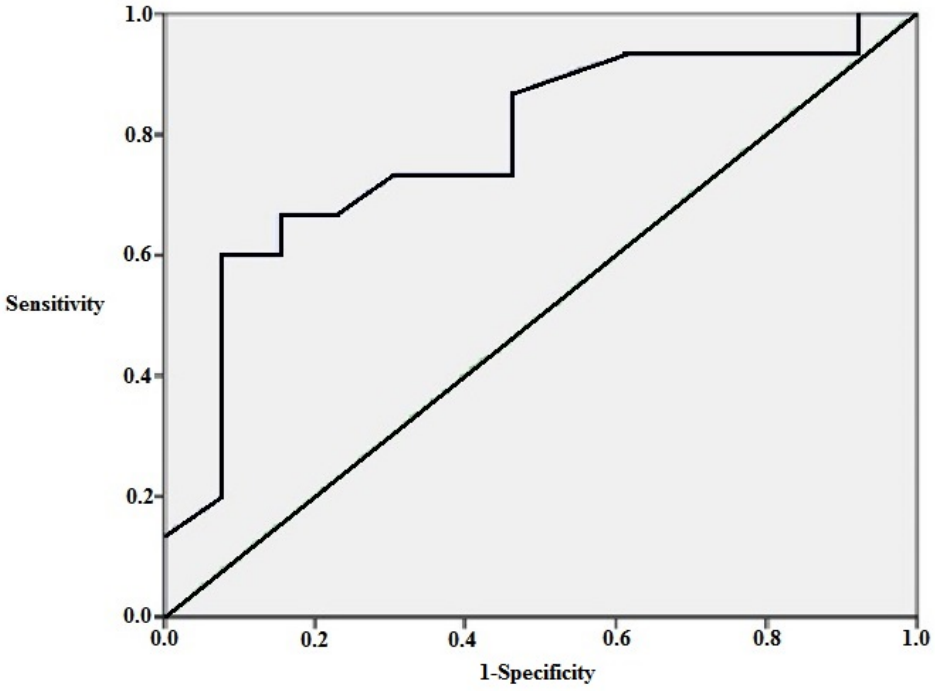
436 **Figure 1** The receiver operating characteristic curve for prediction of emergent cesarean
437 section in pregnancies diagnosed with vasa previa. The curve represents prediction of the
438 probability of emergent cesarean section using the rate of cervical length shortening
439 (mm/week) which yielded an area under the receiver operating characteristic curve of 0.85
440 (95% CI, 0.69-0.99).



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