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Research Article

To study the efficacy of digital and transvaginal ultrasonographic measurement of cervical length in asymptomatic high risk women at POG 16-24 weeks as a predictor of preterm delivery and progesterone and cerclage vs. progesterone alone for short cervical length in prevention of preterm labour

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ABSTRACT

Background: Objectives of current study were (i) To correlate the Cervical Length (CL) measured digitally and by transvaginal sonography (TVS) at 16 to 24 weeks with outcome of pregnancy (ii) Estimate risk of spontaneous preterm labour (PTL) based on CL measurements and (iii) study intervention in short CL and their effect on maternal and neonatal outcome.

Methods: Women with singleton pregnancy at POG 16-24 weeks with history of previous preterm birth or mid trimester abortions were included in the study and subjected to digital assessment of CL followed by TVS measurement. In patients with TVS CL ≤25 mm, intervention in the form of progesterone or cerclage with progesterone was done. The outcome of the pregnancy in the form of delivery before completed 37 weeks or at and after 37 weeks was noted.

Results: Twenty two subjects out of total 153 subjects (14.4%) had preterm delivery. The incidence of preterm delivery in study was 14.4%. Using Receiver Operating Characteristics (ROC) Curve, cut off value of digital CL was found to be 1.5 cm. The sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy of digital CL ≤1.5 cm in prediction of PTL were 72.7 %, 37.4%, 16.3%, 89.1% and 42.5% respectively. Cut off value of TVS CL by ROC curve was found to be 2.85 cm. The sensitivity, specificity, PPV, NPV and accuracy of CL (TVS) of ≤2.85 cm in prediction of PTL is 81.8%, 68.7%, 30.5%, 95.7%, 70.6% respectively. The outcome in form of PTL in 30 subjects, who had TVS CL ≤2.5 cm in both the intervention groups (McDonald stitch with progesterone and progesterone alone) was comparable (P value 0.60 not significant).

Conclusions: The CL, both digitally and by TVS, was inversely correlated with the probability of preterm delivery so that the shorter the cervix, the greater the likelihood of preterm delivery. TVS CL is more predictive of preterm delivery than digital CL when performed between 16-24 weeks in asymptomatic high risk women. Intervention in short CL in form of McDonald's stitch application with progesterone and progesterone alone have similar efficacy for prevention of PTL.

Keywords: Cervical length, Transvaginal sonography, Preterm labour

INTRODUCTION

Preterm delivery is defined as delivery before 37 weeks of gestation. The incidence of preterm births ranges between 10 and 15%. It is the leading cause of perinatal morbidity and mortality and is responsible for 75% of perinatal deaths and when lethal anomalies are excluded, 85% of all neonatal deaths occur in preterm infants.[1]

In order to address the prematurity problem, it is important to identify risk factors like cervical insufficiency, excisional cervical treatment, previous spontaneous preterm birth, rupture of membranes, multifetal gestation, fetal anomaly, polyhydramnios. However, many women who deliver preterm have no known risk factors. Research has focused on combined risk scoring systems that use multiple serum markers, ultrasound and maternal demographic factors to predict preterm birth but these have not been fully validated. Several studies consistently found that shorter the CL, the higher the rate of spontaneous preterm delivery. Digital assessment of the cervix has been commonly used to evaluate women for increased risk of PTL but it is subjective, varies with examiners and underestimates the true anatomic length.

Sonographic measurement of CL can be performed by transabdominal, transvaginal, or transperineal examination. TVS assessment of CL is more reliable because of visibility of cervical canal and internal os including supravaginal portion of cervix.

METHODS

This prospective study was conducted in the department of obstetrics and gynaecology, Kamla Nehru state hospital for mother and child, Indira Gandhi medical college, Shimla. The study was of one year duration from 1st May 2012 to 30th April 2013 and the sample size was of 160, calculated as given below:

$$S = \frac{Z^2 \times (p) \times (1 - p)}{C^2}$$

Where:

Z = 1.96 (95% confidence level)

p = percentage, its value is 0.1

c = confidence interval, its value is 0.05,

The sample size calculated using the above formula was 138. Considering the dropout rate as 15%, value was 160.

The inclusion criteria were women with singleton pregnancy at POG 16-24 weeks with history of previous preterm birth or mid trimester abortions. Exclusion criteria were women with previous cervical operative intervention (Conization, trachelorrhaphy), placenta praevia twins/multiple pregnancy, polyhydramnios, fetal anomaly, induction of labour for medical indications before term. After taking a written informed consent detailed history was taken. Gestational age was determined from the date of the last menstrual period and confirmed by ultrasonography before 20 weeks. After routine antenatal investigations and treatment of any symptomatic vaginal infections, at 16 to 24 weeks cases were subjected to digital assessment of CL followed by TVS measurement .It was performed in the same sitting. Before examination, each patient emptied her bladder and then was placed in dorsal lithotomy position. After digital assessment of CL, the vaginal probe was covered with a sterile condom with a sterile gel curvilinear transvaginal probe (JUST VISTER - 200 Toshiba model 325 A).

The CL was measured in the sagittal plane with the probe in anterior vaginal fornix, visualizing the internal and external os and the endocervical canal as landmarks. The appropriate sagittal view was identified by the location of the triangular area of echodensity at the external os, a V-shaped notch at the internal os, and a faint line of echodensity or echolucency between the two. Undue pressure on the cervix that might artificially increase its apparent length was avoided by first obtaining an apparently satisfactory image, then withdrawing the probe until the image blurred, and finally reapplying only enough pressure to restore the image. Care was taken to ensure that whole length of the cervical canal could be observed and distance from surface of posterior lip to cervical canal was equal to distance of anterior lip to cervical canal.

The cervix was measured in this fashion three times. The CL was the shortest measurement that clearly displayed the criteria described above. This measurement was chosen because first measurements are often 3 to 5 mm longer than subsequent measurements, apparently because of the pressure of the probe required to identify the cervix.

In patients with TVS CL ≤25 mm intervention in the form of progesterone or cervical cerclage with progesterone was done.

Progesterone (natural micronized progesterone) was given in the form of nightly 200 mg vaginal suppository from 24 to 34 weeks. Cerclage procedure used was McDonald's cerclage.

The outcome of the pregnancy in the form of delivery before completed 37 weeks or at and after 37 weeks was noted.

Statistical analysis

The chi-square test, percentile, standard deviation, arithmetic mean, median, correlation coefficient test was used for statistical analysis. Statistical testing was

conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables were presented as mean ± SD, and categorical variables were presented as frequency and percentage. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate.

A Receiver Operating Characteristics (ROC) analysis was calculated to determine optimal cut-off values for digital CL and TVS CL.

The area under the curve, sensitivity, specificity, NPV, PPV and accuracy were calculated to analyze the diagnostic value of all these markers. ROC curve is used to determine optimal cut off value for a test. It is a graph of sensitivity (y axis) vs. 1-specificity (x axis). Area under the ROC curve is an important measure of accuracy of test. If this area is one, test is 100% accurate. ROC curve areas are typically between 0.5 and 1.[2] For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

Out of initial 160 women recruited 153 delivered at KNSH, 5 were lost to follow up whereas 2 had to be iatrogenically induced before term for ante partum haemorrhage and severe PET respectively. The subjects included were in the range of 19-40 years. The mean age of the study group was 26.57 ± 3.33 years (Table 1). Eighty subjects (52.3%) out of 153 were from age group of >24-29 years. Maximum number, i.e., 87 subjects (57%) belonged to urban area and only 66 subjects (43%) belonged to rural area. Out of 153 subjects, maximum i.e. 48 subjects (31%) were educated up to high school. Mean BMI was 21.47 ± 1.3 kg/m^2. Twenty two subjects out of total 153 subjects (14.4%) had preterm delivery and 131 subjects (85.6%) delivered full term. Thus incidence of preterm delivery in study was 14.4%. For every 6 subjects delivering at full term in the study group, there was one preterm delivery. Mean age of subjects delivering preterm was 26.27 ± 3.27 years (P = 0.654 not significant). PTL was significantly higher in professionals and illiterates (P value 0.039 and 0.03 respectively, significant).

PTL was 33.3% (6 out of 18 subjects) in subjects having history of 2 or more than 2 abortions. (P value 0.014). Preterm delivery was highest i.e. 37.5% (9 out of 24 subjects), in subjects having history of 2 or more than 2 previous preterm deliveries (P value 0.0004 significant). Mean CL measured digitally in term and preterm groups were 1.699 ± 0.52 and 1.365 ± 0.516 cm respectively (P value 0.006 significant) showing that shorter the CL greater the likelihood of preterm delivery. Using ROC Curve (Figure 1), Cut off value of Digital CL was found to be 1.5 cm. Area Under Curve (AUC) for digital CL was found to be 0.647 with 95% confidence interval 0.522 to 0.773. The sensitivity, specificity, PPV, NPV and accuracy of digital CL ≤1.5 cm in prediction of PTL were 72.7%, 37.4%, 16.3%, 89.1% and 42.5% respectively.

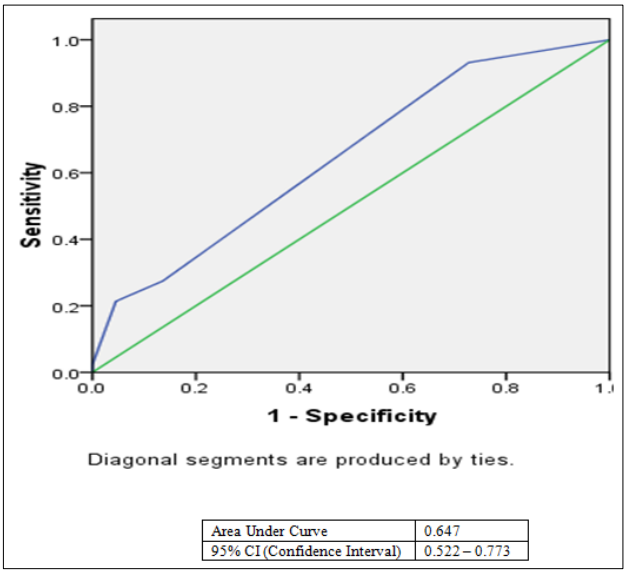

Figure 1: ROC (Receiver operating characteristics) curve for the digital cervical length.

Table 1: Demographic characteristics.

	Total	Preterm	P value
Mean Age	26.57 ± 3.33	26.27 ± 3.27	0.654
Area			
Rural	66	8	0.49
Urban	87	14	0.49
Educational status			
Illiterate	8	4	0.03
Primary	15	1	0.36812
Middle	26	3	0.87288
High	48	6	0.96012
Intermediate	32	3	0.36282
Graduate	20	3	0.4413
Professional	4	2	0.0394
Previous abortion			
0	10	1	0.6818
1	125	15	0.07672
≥2	18	6	0.01468
Previous preterm			
0	24	3	0.77
1	105	10	0.01
≥2	24	9	0.0004

Thirty subjects had CL (TVS) ≤2.5 cm out of which 10 (33%) delivered preterm. Mean TVS CL in term and preterm groups were 3.067 ± 0.531 and 2.455 ± 0.463 cm respectively (P value <0.001 significant) again showing shorter the cervical length greater the likelihood of preterm birth.

Using ROC Curve (Figure 2), Cut off value of TVS CL was found to be 2.85 cm. Area Under Curve (AUC) for

TVS CL was found to be 0.823 which is more than AUC for digital CL (0.647) thereby implying that CL by TVS is more accurate than digital CL. The sensitivity, specificity, PPV, NPV and accuracy of CL (TVS) of ≤2.85 cm in prediction of preterm labour is 81.8%, 68.7%, 30.5%, 95.7%, 70.6% respectively (Table 2). Relative risk for preterm birth at TVS value of 2.85cm was 7.169 whereas for CL of 1.5 cm, measured digitally was 3.45 again showing that cervical length measured by TVS is better predictor of preterm birth.

Table 2: Risk of preterm delivery by cervical length.

Cut off by ROC curve	CL	AUC	Sensitivity	Specificity	PPV	NPV	Significance	Relative risk
Ultrasonographic (TVS)	2.85 cm	0.823	81.8%	68.7%	30.5%	95.7%	<0.001	7.169
Digitally	1.5 cm	0.647	72.7%	37.4%	16.3%	89.1%	0.359	3.45

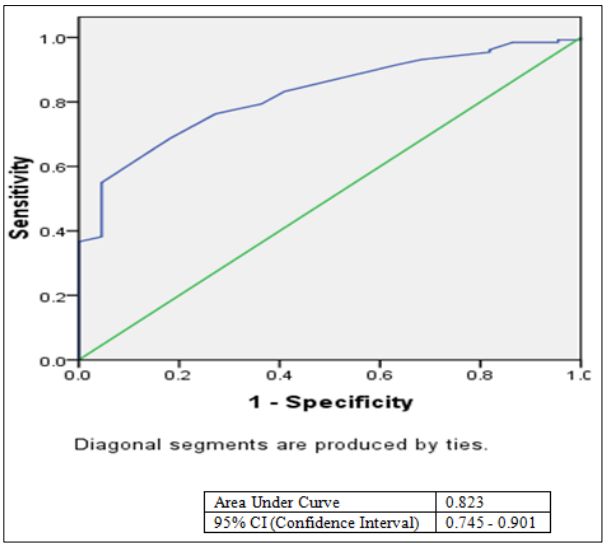

Figure 2: ROC curve for transvaginal sonographic cervical.

The outcome in form of PTL in 30 subjects, who had TVS CL ≤2.5 cm in both the intervention groups (McDonald stitch with progesterone and progesterone alone) was comparable (P value 0.60 not significant) (Table 3).

Table 3: Intervention and preterm labour in short cervical length (≤2.5 cm by TVS).

Intervention	Frequency (n=30)	Pre-term	%	P value
McDonald + progesterone	17	5	29.41%	0.60306
Progesterone	13	5	38.46%	0.60306
Total	30	10	33.33%	

McDonald's stitch application with progesterone in short CL had no additional benefit in maternal and neonatal outcome in comparison to subjects receiving progesterone alone for prevention of preterm labour.

DISCUSSION

In present study, the mean age of the study group was 26.57 ± 3.33 years. The mean age of subjects in present study was slightly less than the studies done by Berghella et al.[3] (1997), Guzman et al.[4] (2001) and Matijevik et al.[5] (2006). This may be attributed to the fact that globally the average age of marriage is between 20-29 years. Mean age of marriage in Himachal Pradesh is 21 years (DLHS-3, 2007-2008).[6] The incidence of preterm delivery in present study was 14.4%. The present study included women with singleton pregnancy at POG 16-24 weeks, with history of previous preterm birth or mid trimester abortions. In studies conducted by Berghella et al.[3] (1997) and Cook and Ellwood[7] (2007) the incidence of preterm birth in high risk women was 18% and 35% respectively, which was high compared to the present study. This could possibly be because both the studies included women with certain very high risk factors like uterine anomalies and with past major surgery, which were excluded in the present study.

In present study PTL was 33.3% (6 out of 18 subjects) in subjects having history of ≥2 abortions whereas it was 12% (15 out of 125) in subjects having history of one abortion and 10.0% (1 out of 10) in subjects having no history of abortion. (p value 0.014 significant). Similarly, studies conducted by Renzo et al.[8] (2011) and Watson et al[9] (2013) also found that history of previous abortions are strongly related to risk of preterm birth (P value 0.01 and <0.001 respectively) Present study showed that subjects with previous preterm delivery had significantly higher preterm delivery in subsequent pregnancy. This was comparable to studies by Agbla et al.[10] (2004), Lo et al[11] (2007) and Crane and Hutchens[12] (2011) where history of previous preterm birth in previous pregnancy is an important predictor of preterm birth in next pregnancy. In both studies, present study and study by Berghella et al.[3] (1997) digital and TVS mean CL in preterm group was significantly shorter than in term group.

In present study using ROC curve, cut off value of digital CL was found to be 1.5 cm. (P value 0.003 significant).

The sensitivity, specificity, PPV, NPV and accuracy of CL ≤1.5 cm in prediction of PTL were 72.7%, 37.4%, 16.3%, 89.1% and 42.5% respectively. According to study done by Berghella et al.[3] (1997) using ROC curve cut off value for prediction of PTL was found to be 1.6 cm which corresponded to 25th percentile of their data. This value was comparable to cut off value found in the present study. P value was not significant in both the studies. Cut off value of TVS CL by ROC curve in present study was found to be 2.85 cm. In contrast, in studies by Berghella et al.[3] (1997) and Guzman et al.[4] (2001) this value was found to be 2.5 cm which was slightly lower than cut off found in present study. Optimal CL cut-off for predicting preterm delivery may vary depending on underlying risk factors. TVS allows for analysis of the prematurity events, accurate depiction of association between risk factors and short cervix.

From present study it was observed that, that TVS CL is more predictive of PTL with P value <0.001. Relative risk for preterm birth at TVS value of 2.85cm is 7.169 whereas for CL of 1.5 cm, measured digitally it is 3.45 again showing that CL measured by TVS is better predictor of preterm birth.

Similar results were seen in study conducted by Berghella et al.[3] (1997) which also showed that by both methods , digital and TVS, length of the cervix was inversely correlated with probability of PTL so that shorter the cervix, greater the likelihood of preterm delivery However, there is much better correlation between shorter CL and higher risk of preterm delivery for ultrasonographic measurements (P value <0.001) Cervical ultrasonography is a better method to evaluate the cervix than digital method because it is more objective (inter observer variability 5% to 10%) and can evaluate the whole length of cervix, especially the upper half including the internal os, where early changes predictive of preterm delivery occur. Whereas digital examination of CL is very subjective (inter observer variability of 52%) not accurate for evaluating the internal os and non-specific.[13]

In present study 30 subjects had TVS CL ≤ 2.5 cm out of which 17 received McDonald stitch and progesterone whereas 13 received only progesterone. Out of 17 who received McDonald stitch and progesterone, five (29.41%) delivered preterm. Out of 13 who received progesterone only five (38.46%) delivered preterm. The outcome in form of PTL in both the interventions was comparable (P value 0.60306 not significant).

Thus far there are no randomised controlled trials that have compared progesterone and cerclage with cerclage alone in women with short cervix, singleton gestation and previous spontaneous preterm birth for prevention of preterm birth.[14]

However, a recently published secondary analysis of the trial by Owen et al.[15] (2009) evaluated the efficacy of cerclage vs. no cerclage in patients with a singleton gestation and previous spontaneous preterm birth who developed a short cervix (<25 mm) in the second trimester while receiving 17α-hydroxyprogesterone caproate. The outcome measures for preterm birth were not significantly different between the cerclage and no cerclage groups.

The authors concluded that cerclage does not offer additional benefit for the prevention of preterm birth in women with a singleton gestation and a cervical length of <25 mm who are receiving 17α-hydroxyprogesterone caproate because of a previous preterm birth.

CONCLUSION

The study has shown that the CL, both digitally and transvaginal sonographically, was inversely correlated with the probability of preterm delivery so that the shorter the cervix, the greater the likelihood of preterm delivery.

TVS CL is more predictive of preterm delivery than digital CL when performed between 16-24 weeks in asymptomatic high risk women.

Hence, TVS is a better method to evaluate cervix than digital examination as TVS is more objective and can also evaluate the upper half of cervix including internal os where early changes predictive of preterm delivery occur.

Optimal cut off values for CL measured digitally and by TVS were 1.5 and 2.85 cm respectively. Women with cervical lengths less than the above cut off values had significantly greater risk of preterm delivery thus, suggesting that the length of cervix is an indirect indicator of its competence Intervention in short CL in form of McDonald's stitch application with progesterone and progesterone alone have similar efficacy for prevention of PTL. Hence, the therapeutic decision making can be based on cost effectiveness as well as on patient's and obstetrician's choice. However, larger studies are required to reach a definitive conclusion.

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Ethical approval: Not required

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