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Full Length Research Paper

The evaluation of Cleopatra I score for predicting preterm birth in subjects with threatened preterm labour

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This work aims to evaluate the Cleopatra I model for the prediction of spontaneous preterm birth (PTB) in subjects having threatened preterm labour. This is a hospital-based prospective observational study done over a period of one year. A total of one hundred and eleven (111) subjects enrolled in the study. Their demographic factors and previous obstetric history were recorded. A cervical length with a cut-off of 25 mm measured by a transvaginal ultrasound was used to evaluate the primary endpoint of the study. Grossly, the preterm delivery rate was 70% in subjects with short cervical length. Funnelling of cervix was associated with 61.1% of those subjects who delivered preterm. Cervical length with a cut-off of ≤2.5 cm showed a sensitivity of 82.1% and a specificity of 37.5% in predicting preterm delivery. In our study, cervical length and funnelling were found to be significantly associated with the outcome of preterm delivery as per the Bivariate analysis. However, on applying logistic regression analysis, funnelling was found to be the only significant association in the prediction of preterm delivery. Thus, the findings of our study could not endorse the observations of the CLEOPATRA I model.

Key words: Risk assessment, premature birth, cervical length measurement.

INTRODUCTION

Preterm birth (PTB) is defined as the birth of an infant before 37 completed weeks of gestation as per the World Health Organization (WHO) (Berghella et al., 2008). The incidence of Spontaneous PTB (sPTB) is 7-12% in pregnancies less than 37 weeks of gestation and about 4% in pregnancies less than 34 completed weeks (Hamilton et al., 2013). Preterm birth is considered to be the second most common cause of demise in younger children and amounting to 60-80% of the neonatal mortality with 75% contributing to severe morbidities (Goldenberg et al., 2008).

There has been no reduction in the incidence of

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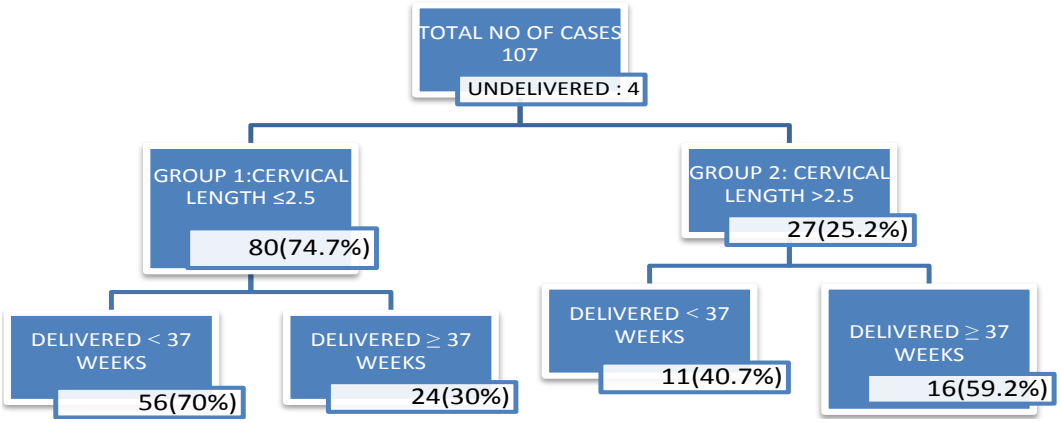

Figure 1. Participant flow.

spontaneous preterm birth despite the advancements in clinical monitoring. Hence, being able to predict the possibility of spontaneous preterm birth at an earlier stage is of utmost importance. Numerous risk scoring systems and biochemical inflammatory markers with screening for various infections such as bacterial vaginosis have been suggested for the prediction of PTL. The modifiable risk factors for preterm birth include short interpregnancy interval, poor maternal weight gain, and low maternal weight. The accuracy of the above said risk factors for the prediction of preterm birth still fall short (Tekesin et al., 2005). The Cleopatra 1 and 2 scoring systems were formulated by Tekesin et al. for symptomatic women who were at risk for preterm delivery. A cervical length of < 2.5 cm at admission and a history of prior preterm delivery were used to create the Cleopatra I score. The Cleopatra II model was further designed using the variables of Cleopatra I model with the inclusion of fetal fibronectin. Fetal fibronectin and prior preterm delivery were associated with greater risk of preterm delivery (Tekesin et al., 2005). This study was undertaken with the following objectives: (i) to evaluate the Cleopatra I model in the prediction of sPTB in subjects admitted with threatened preterm labour and (ii) to assess the role of cervical funnelling as an additional factor in the prediction of preterm birth.

MATERIALS AND METHODS

The study, being a prospective observational study, was conducted in Sir Sayajirao Gaekward (SSG) Hospital and Medical College Vadodara, India over a period of one year with approval from the Institutional Ethics Committee. All women with singleton pregnancy were allowed to participate if they had arrived between 24 weeks to 36+6 weeks gestation with threatened preterm labour. The presence of at least 4 uterine contractions in 20 min or 8 contractions in an hour or any uterine activity with changes in the cervical consistency (at least 50% effacement and 2 cm dilatation) defines threatened PTL. Known gestational age was assigned based on Last Menstrual Period (LMP) /First or early second trimester ultrasound scan. Women with multiple pregnancy, cervical dilatation ≥3 cm, placenta previa, vaginal bleeding of unknown origin, fetal growth restriction, ruptured membranes, pre-eclampsia, suspected fetal asphyxia, major fetal anomaly and medically induced labour were excluded. Demographic characteristics and previous obstetric history were recorded. General and obstetric examination was performed. Height, weight, body mass index (BMI), maternal weight gain during index pregnancy were documented. High vaginal swab was sent. The cervical length at admission and presence of funnelling was documented by using a 7.5 Mhz Transvaginal ultrasound probe based on the technique standardised by the Fetal Medicine Foundation (Certificates of Competence: Available from: http://www.fetalmedicine.com/fmf/training-certification/certificates-of-competence/cervical-assessment). A mean of three measurements was derived.

A cervical length with a cut-off of 25 mms was used to evaluate the primary endpoint of the study, because of its better sensitivity and specificity when compared to a length of 16 mm (Di Renzo et al., 2011). Treatment with tocolytics and corticosteroid was administered to all subjects as per unit protocol. Cervical encirclage was performed if required. The subjects were followed up until they delivered. The primary endpoint of the study was delivery occurring at < 37 weeks of gestation and the secondary endpoints were delivery < 34 weeks of gestation or delivery within 7 days of admission.

Data analysis

Categorical data were indicated as percentages with continuous variables being represented as mean and SD. Diagnostic indices such as Sensitivity, Specificity, Positive and Negative Predictive values were evaluated. The area under the ROC curve (AUC) was used to depict the discriminative ability of cervical length. Logistic regression was applied to analyze the relationship between independent and dependent variables.

RESULTS

Hundred and eleven (n=111) subjects fulfilling the inclusion criteria were enrolled in this study. Hundred and seven (107/111) subjects were included for the purpose of final analysis excluding those four women who had not delivered during the defined study period. Figure 1 depicts the flow of participants in the study. Table 1

Table 1. Demographic characteristics of study population.

S/N	Demographic characteristic	Group1: Cervical length ≤2.5 cm (N=80)	Group 2: Cervical length >2.5 cm (N =27)	p-value
1	Maternal Age in years (Mean and SD)	24.06 (±4.3)	24.8 (±4.2)	0.4
2	Gestational age at admission (Mean and SD)	33 weeks (±2 weeks 6 days)	32 weeks 5 days (±3 weeks)	0.8
3	Gestational Age at delivery (Mean and SD)	35 weeks 4 days (±3 weeks 1 day)	37 weeks1 day (±2 weeks 2 day)	0.02
4	Nullipara (No, %)	39 (48.7)	13 (48.1)	0.8
5	Previous H/O PTL (%)	07 (8.75)	00	0.2
6	Delivery< 37 weeks (%)	56 (70)	11 (40.7)	0.01
7	Examination to delivery interval (days) (Mean and SD)	18.3 (±18.3)	29.9 (±19.3)	0.005

compares the demographic characteristics of the study population in terms of mean and standard deviation. Subjects with cervical length ≤2.5 cm will be designated as Group 1 and subjects with cervical length > 2.5 cm will be designated as Group 2 for the purpose of this analysis. The table shows that there was no statistical difference between the two groups in terms of maternal age and gestational age at admission. Mean gestational age at delivery in Group 1 was 35 weeks 4 days (±3 weeks 1day) and in Group 2 it was 37 weeks 1 day (±2weeks 2day) expressed in terms of Mean and SD; this difference in gestational age at delivery was significant at p value of 0.02. The examination to delivery interval in Group 1 was 18.3 ± 18.3 days and in Group 2 it was 29.9± 19.3 days. This observation was highly significant at a p value of 0.005. Sixty-seven subjects delivered preterm. Of these, 56 subjects (70.0%) belonged to Group 1(N=80) and 11 subjects (40.7%) belonged to Group 2 (N=27). This observation of delivery before 37 weeks was highly significant with a p value of 0.01

Table 2 is an interpretation of the cervical characteristics of the study population using Bivariate analysis. Out of 107 subjects enrolled, 67 subjects (62.6%) had preterm delivery. Of these 67, fifty-six subjects (83.5%) had a cervical length of ≤2.5cms and 11 subjects had a cervical length greater than 2.5 cm. Among the 40 subjects (37.4%) who had a term delivery, 24 subjects had a short cervix (≤ 2.5 cm) and 16 subjects had a cervical length greater than 2.5 cm. This difference was significant with a p value of 0.013. Forty-one subjects (85.1%) with presence of cervical funnel delivered preterm. This observation was statistically significant with a p value of <0.0001.

Table 3 describes the obstetric characteristics of our study population. Out of 80 subjects who had a cervical length ≤2.5 cm, 70 subjects (87.5%) had vaginal delivery and 68 subjects (85%) went into spontaneous labour. This observation was not statistically significant. The number of NICU admissions in group 1 was 28 (35%) and in group 2 this number was 05 (18.5%). This observation was found to be statistically significant with a p value of 0.01. Table 4 and Figure 2 show the predictive values for cervical length in preterm delivery. Cervical length of ≤2.5 cm had a sensitivity of 83.5% (95% CI 72.5, 91.5) and a negative predictive value of 59.2% (95%CI 42.9,73.7) in the prediction of preterm delivery. Table 5 shows the logistic regression of factors affecting the outcome in study population. On bivariate analysis, cervical length and funnelling were found to be significant. When logistic regression was applied, only funnelling was found to be significant at an OR of 25.3 (95% CI 5.3, 119.6) and p value < 0.0000

DISCUSSION

Comparison of study results with Cleopatra study

Our study on 107 subjects showed that cervical length and funnelling were found to be significantly associated with the outcome of preterm delivery in the Bivariate analysis. However, on applying logistic regression analysis, funnelling was found to be the only significant association (p<0.0000). Cervical length ≤ 2.5 cm did not achieve statistical significance. These results do not match those of Tekesin et al. (2005) in the CLEOPATRA 1 study, according to which previous preterm delivery and cervical length had a statistical significance. This difference in observation between our study and the Tekesin et al. (2005) study could be because of the smaller sample size in our study as

Table 2. Cervical characteristics in the study population.

Variable (Cervical characteristics)	Group	Delivery <37 weeks (Pre-term delivery, %) (N=67)	Delivery ≥37 weeks (Term delivery, %) (N=40)	P value
Cervical length	≤2.5 cm >2.5 cm	56 (83.5) 11 (16.4)	24 (60) 16 (40)	0.013
Funnelling	Present Absent	41 (61.1) 26 (38.8)	5 (12.5) 35 (87.5)	<0.0001
Bishop score	≥4 <4	51 (76.1) 16 (23.8)	26 (65) 14 (35)	0.31
H/o Previous preterm delivery	Yes No	06 (8.9) 61 (91)	01 (2.5) 39 (97.5)	0.367

Table 3. Obstetric characteristics of the study population.

Obstetric characteristics	CL ≤ 2.5 (Group 1) (N=80)	CL >2.5 (Group 2) (N=27)	P value
Mode of delivery			
Vaginal (%) CS (%)	70 (87.5) 10 (12.5)	23 (85.1) 04 (14.8)	0.98
Type of labour			
Spontaneous (%) Induced (%)	68 (85) 12 (15)	23 (85.1) 04 (14.8)	0.77
Neonatal outcomes			
Birth weight (Mean-SD)	2135 (±558.1)	2351.8 (±516.9)	0.07
NICU admission (No, %)	28 (35)	05 (18.5)	0.01
Duration of NICU stay in days (Mean-SD)	4.78 (±3.08)	4.4 (±1.14)	0.53
Duration of hospital stay in days (Mean-SD)	4.96 (±2.92)	4.18 (±2.0)	0.2

Table 4. Predictive value of cervical length.

Cervical length	Preterm delivery (%)	Term delivery (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Positive LR (95% CI)
≤2.5	56 (83.5)	24 (60)	83.5%	37.5%	70%	59.2%	1.39%
>2.5	11 (17.9)	16 (37.5)	(72.5,91.5)	(24.86,56.6)	63.9,75.4)	(42.9,73.7)	(1.06, 1.83)

compared to the 170 subjects in the Tekesin study. In our study as well as in the Tekesin et al. (2005) study there were 6 subjects with past history of preterm birth who delivered before 37 weeks of gestation. The CLEOPATRA study did not include funnelling as an end point. A cervical length of less than equal to 2.5 cm had a sensitivity of 83.5% and a specificity of 37.5% in the prediction of preterm delivery in our study. These findings are quite similar to those of Schmitz et al. (2008) who in their study found that a cervical length of less than 2.5 cm has a sensitivity, specificity, Positive Predictive Value and Negative Predictive Value of 85, 48, 14 and 97% in the prediction of delivery within 7 days of admission (Schmitz et al., 2008). Similarly, Sotiriadis et al. (2010) in a meta-

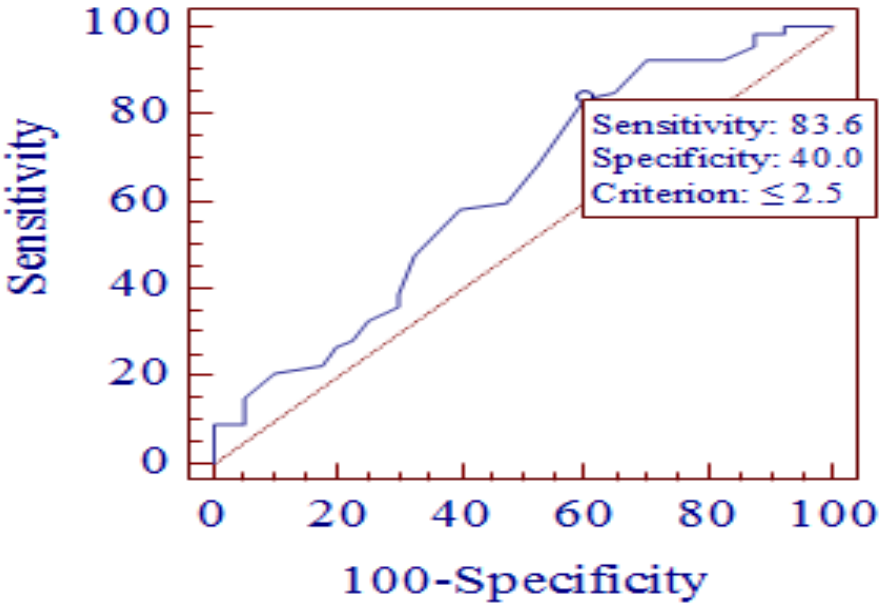

Figure 2. ROC curve of accuracy of cervical length in prediction of delivery before 37 weeks.

Table 5. Logistic Regression of factors affecting outcome in the study population.

Variable (Cervical Characteristics)	Odds ratio	95 % CI		P value
Funnelling	25.3601	5.3753	119.6463	0.0000
Cervical Length	1.1465	0.3993	3.2923	0.799
H/o Previous preterm delivery	2.7012	0.2438	29.9317	0.418

analysis of 28 studies, found that on raising the cervical length cut-off to 25 mm, the sensitivity and specificity improved to 78 and 71% respectively (Sotiriadis et al., 2010).

Funelling as a predictor of preterm labour

Our study found that funnelling has a significant association with preterm birth. Ville and Rozenberg (2018) in his study, showed that preterm labor was significantly associated with the presence of funnelling in symptomatic women with improved sensitivity, specificity, PPV, and NPV (Ville and Rozenberg, 2018).

Saade et al. (2018) found that the presence of a funnel or debris was highly associated with preterm birth at less than 37 weeks of gestation. The regression analysis studies conducted by them concluded that the presence of intra-amniotic debris was associated with increased risk of PTB < 34 weeks of gestation irrespective of the cervical length. Positive fetal fibronectin, short cervix and amniotic fluid sludge were independently associated with preterm birth in the study conducted by Spiegelman et al. (2016) on preterm birth. Cervical funnelling was not independently associated with spontaneous preterm birth in twins.

A serial transvaginal cervical ultrasound examination by Andrews et al. showed that a cervical length less than 10th centile (2.2 cm) or funnelling at the internal os was significantly associated with preterm delivery at a p value of <0.001(Andrews et al., 2000).

Demographic factors and preterm birth

The findings of our study with respect to demographic characteristics are similar to those of other studies. Liren Hiersch et al, in their cohort study of women who presented with preterm labour, found a statistically significant difference in the gestational age at admission (33 weeks 2 days) and their delivery interval within 7 days of admission at a p value of <0.001 respectively (Hiersch et al., 2014). in their randomised control trial found that 77.3% of those who delivered preterm went into spontaneous labour (Palacio et al., 2018). Daskalakis et al. (2005) in their study on 172 subjects, found that

cervical length of less than 2.5 cm with history of previous preterm delivery had 2.7 times greater chances of delivering preterm.

Conclusion

In this study, the presence of cervical funnelling was significantly associated with spontaneous preterm birth. A Cervical length of ≤ 2.5 cm and the history of previous preterm delivery were not found to have an independent association with preterm birth, which is different from the original Cleopatra I study where both cervical length and previous preterm delivery were associated with a higher risk of preterm delivery .Thus, the findings of our study could not endorse the observations of the Cleopatra I model.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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