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"CERVICAL GLAND AREA AS A POTENTIAL PREDICTOR OF PRETERM DELIVERY USING TRANSVAGINAL ULTRASONOGRAPHY"

Obstetrics & Gynaecology

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ABSTRACT

Preterm labor is a significant contributor to perinatal morbidity and mortality, and its prediction is crucial for effective management. This prospective cohort study involved 200 singleton pregnant women with a history of spontaneous preterm labor (SPTL), second-trimester abortion in a previous pregnancy, or lower abdominal pain during the current pregnancy. Transvaginal ultrasound examinations were conducted between 12-28 weeks of gestation, measuring cervical length and assessing the presence of cervical gland area (CGA). The study aimed to evaluate the relationship between these factors and SPTL occurring before 35 and 37 weeks of gestation, using JAMOVI version 2.3.12. The key findings of the study are as follows: The mean cervical length was 37.2 + 7.8 mm, with a range of 8.5 mm to 63.3 mm. Cervical lengths of 16 mm or less were significantly associated with SPTL before both 35 and 37 weeks of gestation. CGA was present in the majority of patients (88.5%). The absence of CGA was significantly related to SPTL before 35 and 37 weeks of gestation. Women with absent CGA had shorter cervical lengths compared to those with present CGA ($p<0.001$). In conclusion, the study suggests that the presence or absence of cervical gland area (CGA) may serve as a valuable predictor for SPTL. However, further research is needed to confirm the significance of CGA in predicting SPTL.

KEYWORDS

Preterm, Ultrasonography, Cervical length

INTRODUCTION:

Preterm delivery, characterized by childbirth occurring before the full 37 weeks of gestation, is attributed to a diverse array of factors, encompassing both individual and environmental influences[1]. This multifaceted nature presents considerable challenges in forecasting and averting preterm birth within the realm of antenatal care. Preterm birth stands as the foremost contributor to perinatal health complications and fatalities. Infants born prematurely face an elevated risk of experiencing conditions such as respiratory distress syndrome, intraventricular haemorrhage, sepsis, necrotizing enterocolitis, as well as enduring long-term developmental challenges[2-6].

Preterm delivery (PTD) is a significant public health concern, as it serves as a crucial determinant of morbidity and is the primary cause of neonatal mortality. The occurrence of PTD has been on a gradual rise, even in developed nations, and it continues to pose a substantial concern for the health and well-being of fetuses and newborns[7-9]. In recent years, there has been an increasing emphasis in published literature on the significance of an additional morphological ultrasound marker for PTD, referred to as the "cervical gland area" (CGA)[10-12]. Cervical length shortening is an important indicator of cervical maturation and a valuable factor in assessing PTL. However, it is just one of the several signs that indicate cervical maturation. Despite numerous studies on cervical length, the prevalence of preterm birth remains high, indicating a need for further research on other cervical changes. One such alteration in the cervical maturation process is the disappearance of the CGA. This process of physiological cervical ripening involves changes in the composition of collagen and proteoglycans. Cervical maturation involves collagen disorganization, decreased collagen concentration, and increased water content. This process leads to the disappearance of the cervical gland area (CGA) in ultrasound images, with changes in water content and biochemical factors playing a significant role[10,13,14].

Cervical length, determined through vaginal sonography, and the presence of fetal fibronectin (fFN) secretion in the cervix and vagina have been put forward as highly effective predictors of preterm delivery (PTD). A short cervix is known to predict preterm delivery (PTD) with sensitivity ranging from 69% to 83% and specificity ranging from 69% to 88%. However, it typically has a relatively low positive predictive value (PPV) in the range of 22% to 54% when dealing with symptomatic women[15-18]. This study aims to evaluate the link between PTD and the measurement of cervical length, cervical funnelling, and the absence of CGA detection.

METHODS

Study Design, Sample Size And Source Of Data:

This was a cross sectional study carried out on 78 preterm women referred for prenatal care at Department of Radiodiagnosis, Sri Devaraj Urs Medical College over period of one year from July 2022 to July 2023. The sample size was calculated based on previous study conducted by Marsoosi V et al[19].

Inclusion Criteria:

1. Pregnant Women with gestational age between 12 – 24 weeks.
2. Singleton or Multiple Pregnancies
3. Age between 18-40 years.
4. Who are willing to give informed written consent.
5. Any history of spontaneous PTL/ spontaneous abortion in second trimester in past pregnancy.

Exclusion Criteria:

1. Pre-existing Preterm Labor
2. Gestational age more than 28 weeks
3. Known Cervical Insufficiency
4. Multiple Fetuses with Discordant Growth
5. Fetal Anomalies
6. Severe Medical Conditions (e.g., severe hypertension, diabetes)
7. Women who have had recent cervical procedures (e.g., cervical cerclage or cervical conization)
8. Those who are not willing to give informed written consent.

Method Of Data Collection:

The study adhered to the Helsinki Declaration (revised 2013) guidelines and obtained approval from the Medical Ethics Committee of our hospital. Informed consent was obtained from all participants in the study.

In accordance with the criteria mentioned earlier, our study included a total of 78 patients. We collected comprehensive clinical and obstetric history. All participants underwent transvaginal ultrasound examination between the 14th and 28th week of gestation to evaluate cervical length, cervical funnelling, and CGA. Notably, no digital examination was conducted before the ultrasound examination.

Transvaginal ultrasound assessments were conducted using endocavitary transducers. Just before commencing the ultrasound examination, patients were instructed to ensure their bladders were fully emptied. Following this, the pregnant women were positioned in the dorsal lithotomy position. During the examination, the participants were required to have empty bladders. Cervical length measurements were taken in the sagittal view after visualizing both the internal and external orifices within the same plane. Simultaneously, the presence of the cervical gland area (CGA) was assessed. Cervical length was measured three times, and the shortest distance between the external and internal orifices was recorded. Cervical funnelling was defined as the widening of the internal orifice to a width greater than 5 mm[20].

The cervical gland area was characterized as a hyperechoic or

hypoechoic zone surrounding the cervical canal, which aligns with the histological representation of the CGA[10]. If an echogenic or hypoechogenic area surrounding the cervical canal was observed, it was indicative of the presence of CGA. Following this criterion, the pregnant women were categorized into two groups depending on whether CGA was present or absent.

Statistical Analysis:
The data collected was analysed using JAMOVI version 2.3.12. Normality of the data was assessed by Kolmogorov Smirnov test. Socio-demographic variables were analysed in terms of mean, standard deviation (SD), frequency (n) and percentage (%). Chisquare test was used for categorical variables. Student t test was performed to analyse difference between absent and present CGA groups. p-value of <0.05 was taken as statistically significant. Data results were represented in the form of tables and figures. We conducted both univariate and multivariate logistic regression analyses to explore the association between cervical indicators (cervical length, cervical funnelling, CGA) and the occurrence of spontaneous preterm labor (SPTL) before 35 and 37 weeks of gestation.

We treated SPTL before 35 and 37 weeks of gestation as binary outcome variables. To account for potential confounding factors, multivariate analyses were employed, including variables such as age, gravidity, history of preterm labor (PTL), history of abortion, and the gestational age at the time of ultrasound examination.

Furthermore, we determined the cutoff value for cervical length using the receiver operating characteristic (ROC) curve. The area under the curve, along with its 95% confidence interval, was reported as an indicator of cervical length's predictive capability for SPTL. A significance level of p-value<0.05 was considered statistically significant.

RESULTS:
A total of 78 pregnant women were entered into the study. The mean age of patients was 28.6 + 4.5years. The mean gestational age at ultrasound examination time was 21.7 + 2.9 weeks. Other baseline characteristics between CGA absent and present groups are shown in table I. Out of 78 patients 69 (88.46%) were CGA present group and 9 (11.54%) were CGA absent group. Among baseline characteristics only cervical length was statistically significant between two groups (p < 0.05).

Table I: Demographic characteristics between two groups:

Variables	CGA present group	CGA absent group	p-value
Age (year)*	28 + 4.5	26.5 + 3.3	0.33
Preterm labour history**	7 (10.1%)	3 (33.3%)	0.08
Abortion history**	6 (8.7%)	0 (0.0%)	0.36
Abdominal pain**	61 (88.4%)	8 (88.9%)	0.97
Cervical length (mm)*	38.6 + 6.9	23.4 + 7.5	< 0.001
Gestational age at USG exam (week)*	21.6 + 2.9	22.4 + 3.6	0.45

CGA: Cervical Gland Area
*Represented as Mean+Standard deviation
** Represented as frequency (n) and percentage (%), n (%)

Among total 78 patients, 5 (6.4%) presented SPTL before 37weeks of gestation. The mean cervical length was 37.2 + 7.8 mm, the shortest cervical length was 8.5mm and longest was 63.3mm. We took 16 mm as cut-off value by ROC curve. The area under the curve is shown in fig 1.

Out of the patients, 3 (2.6%) had a cervical length of less than 16 mm. Significantly, short cervical lengths (≤16mm) were linked with SPTL before both 35 and 37 weeks of gestation, as indicated in Tables II and III. Additionally, cervical funnelling was observed in 8 (10.2%) women. This morphological characteristic demonstrated a statistically significant association with SPTL before 35 weeks of gestation, although it did not exhibit a similar relationship with SPTL before 37 weeks, as shown in Tables II and III.

Table II: Univariate and multivariate regression analyses of three sonographic markers for spontaneous preterm labour before 37 weeks gestation

Variable	Unadjusted odds		Adjusted odds	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Cervical length	0.80 (0.69 – 0.91)	0.001	0.80 (0.69 – 0.91)	0.05
Funnelling	5.2 (1.1 – 18.9)	0.45	3.6 (0.9 – 85.3)	0.76
Cervical gland area	187.5 (23.8 – 4317)	<0.001	313.4 (45.7 – 9584)	<0.001

OR: Odds ratio, **CI:** Confidence interval
Based on logistic regression analyses.

In 69 (88.5%) patients of the total participants, CGA was present. However, in 9 patients of the entire study population, CGA was absent. This subset included two women who experienced SPTL before 35 weeks of gestation and three women who experienced SPTL before 37 weeks of gestation. The absence of CGA demonstrated a significant association with SPTL before both 35 and 37 weeks of gestation, as indicated in Tables II and III.

Table III: Univariate and multivariate regression analyses of three sonographic markers for spontaneous preterm labour before 35 weeks gestation

Variable	Unadjusted odds		Adjusted odds	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Cervical length	0.89 (0.70 – 0.98)	0.002	0.90 (0.86 – 0.99)	0.003
Funnelling	9.8 (2.5 – 89.5)	0.05	2.3 (1.1 – inf)	0.002
Cervical gland area	136.8 (23 – inf)	<0.001	16.7 (2.3 – inf)	<0.001

OR: Odds ratio, **CI:** Confidence interval
Based on logistic regression analyses.

Regarding predictive values, for SPTL before 35 weeks of gestation, the sensitivity was 33.0% and the specificity was 97.8%. The corresponding positive predictive value (PPV) was 39.5% and the negative predictive value (NPV) was 95.7%.

For the prediction of SPTL before 37 weeks of gestation, the sensitivity was 22.4%, and the specificity was 98.6%. The positive predictive value (PPV) was 44.2%, and the negative predictive value (NPV) was 96%. Our findings indicate that women with an absent CGA had significantly shorter cervical lengths compared to those with a present CGA (p<0.001) as shown in Table I.

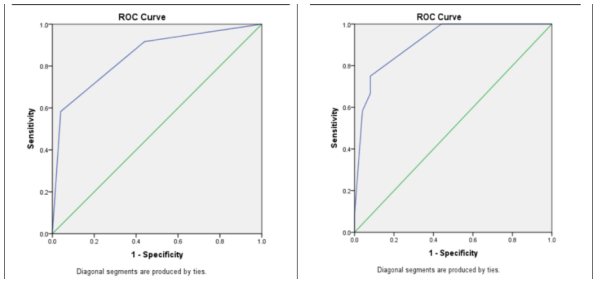

Fig 1: ROC curves were constructed to establish the cutoff values for cervical length in predicting SPTL before 35 weeks (on the left) and 37 weeks (on the right).

DISCUSSION:
The findings of our study revealed a significant increase in the odds of preterm labor (PTL) occurring before 35 and 37 weeks of gestation among pregnant women with an absent CGA during the 12 - 28week gestational period, as indicated in both univariate and multivariate exact logistic regression analyses. Additionally, we observed that women with an absent CGA had significantly shorter cervical lengths compared to those with a present CGA. These results align with the findings of several other studies, emphasizing the importance of CGA as a predictive factor for preterm labor10, 20-23. Fukami and colleagues assessed the correlation between cervical length and CGA at 16-19 weeks of gestation concerning early preterm labor (PTL) and reported a specificity of 99.8% and a sensitivity of 75% for early PTL prediction using CGA21. Asakura and colleagues reached the conclusion that in patients with threatened preterm labor (PTL), having a short cervical length in the absence of CGA is an independent predictor for PTL. They also noted that the detection rate of CGA exceeded 90% between 16 and 31 weeks of gestation but progressively declined to 16% by the 40th week of gestation22.

Pires conducted an assessment of the relationship between spontaneous preterm labor (SPTL) and factors such as cervical length, the absence of CGA, and cervical funnelling in a general population. Their findings indicate that the absence of CGA can serve as a significant ultrasound indicator for SPTL23.

While previous studies have uniformly recognized the absence of CGA as a noteworthy marker for predicting preterm labor (PTL), it is important to note that the incidence of absent CGA varies significantly among these studies. For example, Yoshimatsu et al. reported an incidence of 0.36% between 16-19 weeks of gestation11, whereas Pires and colleagues found an incidence of 2.7% between 21-24 weeks of gestation23, and our study observed an incidence of 11.5% between 12-28 weeks of gestation. These differences in the occurrence of absent CGA among these studies may be attributed to variations in study design and the selection of study subjects.

When it comes to various cervical markers, there is a lack of consensus. Take, for instance, the measurement of cervical length, which is widely utilized. There is no universally agreed-upon cutoff for what constitutes a "short cervix." The range can span from less than 15 mm to as much as 35 mm, as indicated in previous research11, 20, 24-27. In our study, we identified a cutoff value of 16 mm as a means of predicting PTL.

In a similar vein, cervical funnelling is frequently associated with uterine contractions and, therefore, might not be deemed a reliable predictor of PTL. In contrast, CGA provides a direct reflection of cervical maturation and is typically less subjective11. Yamaguchi and colleagues conducted an evaluation of CGA and cervical length at 37-38 weeks of gestational age and demonstrated that the combination of CGA and cervical length serves as a valuable predictor for the onset of labor within a week in full-term pregnant women28.

Several studies have underscored the growing significance of CGA as a predictor of preterm labor (PTL) 10,11, 22,23. However, there is a persistent challenge in early prediction of SPTL that continues to engage researchers. More research endeavors are warranted to corroborate the importance of the absence of CGA in predicting PTL. In our study, the rate of women delivering before 37 weeks of gestation was only 6.4%, which appears to be quite low. The remarkably low rate of preterm deliveries, at only 3.5% in our study, can be attributed to the inclusion criteria we used. A substantial portion of our study population presented with lower abdominal pain, which is a common occurrence during pregnancy and often unrelated to cervical shortening or dilation. Consequently, our population was not considered at high risk for preterm labor (PTL).

Additionally, the implementation of interventions such as bed rest, progesterone administration, and cerclage, when deemed necessary, could explain the low rate of preterm births in this study. However, it's important to acknowledge some limitations of our study. The small sample size resulted in wide and less interpretable confidence intervals (CIs), which could be rectified by including a larger number of subjects in future studies or through multicenter research collaborations. Another limitation was the relatively low sensitivity values when establishing the cutoff value for cervical length. We recommend conducting more comprehensive studies on high-risk population groups and the general population, involving larger sample sizes, to provide further clarity on the reliability of absent CGA as a predictor of PTL.

CONCLUSION:

In summary, our study findings reveal a significant link between the absence of CGA during the 12 - 28week gestational period and the occurrence of SPTL before both 35 and 37 weeks of gestation. The absence of CGA appears to be indicative of cervical maturation and has the potential to serve as a robust predictor of preterm labor, although confirmation through additional research is needed.

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