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Original Article

Fetal Adrenal Gland and Adrenal zone parametres- Novel Predictors of Preterm Labour

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ABSTRACT

Background: Preterm birth is a significant global health concern, contributing to neonatal morbidity and mortality. Fetal adrenal gland volume and fetal adrenal zone width and depth ratios have emerged as potential biomarkers for predicting preterm birth.
Aim: To assess the role of fetal adrenal gland volume and fetal adrenal zone parameters in predicting preterm labor.
Methods: A cross-sectional study was conducted at Gandhi Hospital, Hyderabad, involving 100 singleton pregnant women. All women who presented in the antenatal OPD at 32 weeks period of gestation with signs and symptoms of preterm labour, were subjected to 2D ultra sonographic measurement of
1. corrected fetal adrenal gland volume (cFAGV)
2. fetal adrenal zone width ratio
3. fetal adrenal zone depth ratio
The cohort was followed upto delivery to know the number of preterm and term deliveries and the parameters of the two groups were compared.
Results: Among the 100 women, 39% had preterm deliveries. The mean cFAGV was significantly higher in the preterm birth group (397.04 mm^3/kg) compared to the term birth group (335.41 mm^3/kg) with a p value of <0.001. However the difference of mean fetal adrenal zone width ratio and that of mean fetal adrenal zone depth ratio were not statistically significant. ROC analysis showed that cFAGV had the highest predictive accuracy (AUC=0.7321) with sensitivity and specificity of 71.79% and 75.41% respectively.
Conclusion: cFAGV is a significant predictor of preterm labor demonstrating strong predictive accuracy and its incorporation in clinical practice could enhance early detection and timely intervention, potentially improving neonatal outcomes.

Keywords: *Preterm labour, (cFAGV), Fetal adrenal gland, Ultrasonography.*

INTRODUCTION

Preterm labour (PTL), defined as the onset of labour before 37 completed weeks of gestation, is a leading cause of neonatal morbidity and mortality worldwide. According to the World Health Organization (WHO), preterm birth affects approximately 15 million infants annually, accounting for 10% of all live births globally (1). The consequences of preterm labour (PTL) extend beyond neonatal mortality, as surviving preterm infants are at higher risk for chronic health issues such as neurodevelopmental disabilities, respiratory complications, and impaired cognitive function (2). Despite advances in obstetric care, preterm birth remains the leading cause of death in children under five years of age, contributing to nearly one million deaths annually (3) India, bears the highest burden of preterm births, with an estimated 3.5 million preterm deliveries annually (4). This accounts for nearly a quarter of the global preterm birth burden. The prevalence of PTL in India is estimated to be around 13%, (5). In these settings, early prediction of PTL can facilitate timely referral, appropriate interventions, and better neonatal outcomes.

However, current methods of predicting PTL, including cervical length measurements and biochemical markers, have limitations in sensitivity and specificity, underscoring the need for innovative, reliable, and non-invasive predictive tools (6). The fetal adrenal gland has recently emerged as a potential marker for predicting PTL. The adrenal gland plays a critical role in the initiation of labour by producing cortisol, which are pivotal in the parturition process (7).

The placental clock hypothesis suggests that the fetus determines the timing of parturition through the release of CRH, which activates the maternal and fetal hypothalamic-pituitary-adrenal (HPA) axes (8). This hormonal cascade stimulates fetal adrenal gland enlargement and increased production of cortisol, estrogen and progesterone, and prostaglandins, ultimately resulting in labour initiation (9).

Current diagnostic methods primarily rely on clinical assessment, ultrasonographic evaluation, and biochemical markers. The clinical criteria for PTL diagnosis include regular uterine contractions accompanied by cervical changes, such as effacement and dilation, before 37 weeks of gestation (10). Transvaginal ultrasonography (TVS) is widely used to measure cervical length, with a shorter cervical length being a strong predictor of PTL risk (11). Additionally, fetal fibronectin (fFN) testing, which detects the presence of fFN in vaginal secretions, has emerged as a valuable biochemical marker for PTL. The role of FAGV as a diagnostic tool for PTL is gaining attention due to its non-invasive nature and high predictive value. Ultrasonographic measurement of FAGV and adrenal zone parameters, such as the width-to-depth ratio, has been shown to be more sensitive and specific than traditional markers like cervical length (4)

Aim:
To assess the role of fetal adrenal gland volume and fetal adrenal zone parameter measurement in predicting preterm labour.

METHODS
This study is a cross-sectional observational study conducted at a tertiary care hospital in Hyderabad. The study was approved by the Institutional Ethics Committee. Written informed consent was got from all the subjects. Confidentiality of patient data was maintained throughout the study, and participation was voluntary.

Convenience sampling was employed to recruit patients from the obstetric outpatient department and emergency units based on their eligibility and willingness to participate. A total of 100 participants meeting the inclusion and exclusion criteria were enrolled in the study.

The Inclusion criteria were:

- Pregnant women above years age.
- Singleton pregnancies at 32 weeks of gestation or beyond.
- Women presenting with symptoms of preterm labor.
- Women who gave consent and agreed to follow-up.

The Exclusion criteria were:

- Pregnant women with suspected fetal growth restriction.
- Those with medical complications, like hypertension, preeclampsia, diabetes, and thyroid diseases.
- Women with preterm premature rupture of membranes .
- Pregnancies with fetal anomalies or placenta previa.

After obtaining informed consent, eligible participants underwent 2D ultrasonographic evaluation to measure the corrected fetal adrenal gland volume (cFAGV) and related parameters. The fetal adrenal zone width ratio (w/W) and depth ratio (d/D) were calculated. Ultrasound was performed at the time of presentation and repeated at regular intervals if the participants remained undelivered. Participants were followed up until delivery, and the outcomes were recorded.

Data were collected through structured proformas that included demographic details, clinical history, ultrasound measurements, and delivery outcomes.

The primary study tool was a 2D ultrasound machine equipped with high-resolution probes to measure fetal adrenal gland and zone dimensions. The fetal adrenal zone was identified as a well defined echogenic area within the gland. For the whole fetal adrenal gland the length(L), width(W) and depth(D) were recorded and for the fetal zone the corresponding parameters (l, w and d) were obtained. Length (L and l) was assessed in transverse or sagittal sections, width (W and w) in transverse or coronal sections and depth (D and d) in sagittal or coronal sections. (5)

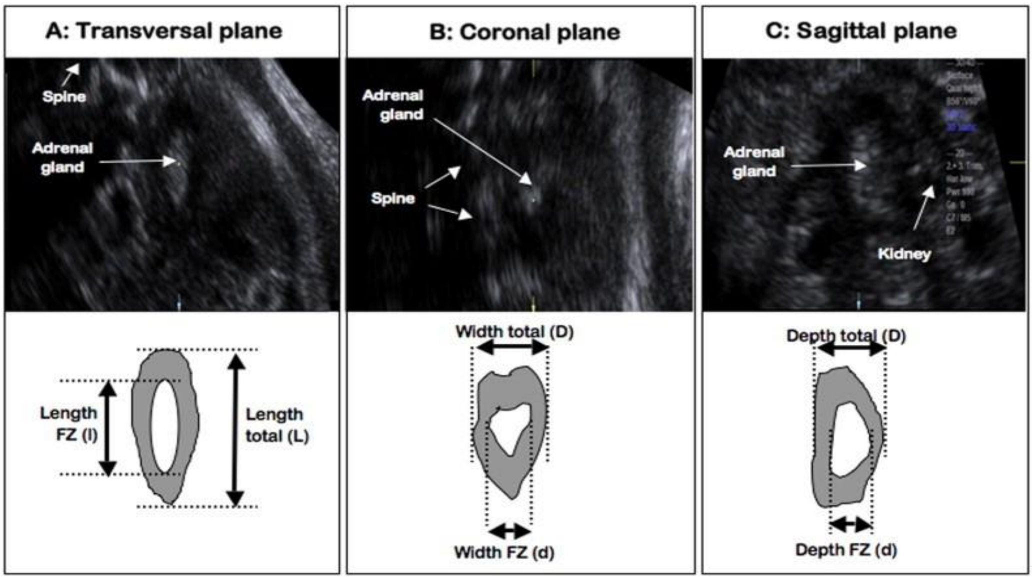


Table / Figure 1: Methodology of measurement of the whole adrenal gland and the fetal zone (5)

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS software (version 22). Descriptive statistics, including means and standard deviations, were calculated for continuous variables. Categorical variables were summarized as frequencies and percentages. Chi-square tests and independent t-tests were used to compare groups. Receiver operating characteristic (ROC) curve analysis was performed to determine the predictive accuracy of cFAGV, with sensitivity and specificity values calculated. A p-value of <0.05 was considered statistically significant.

RESULTS

MATERNAL AGE: The most frequent age categories were 21-25 years and 26-30 years, each comprising 39% of the total participants. Participants aged below 20 years and above 30 years accounted for 11% each, indicating a relatively young cohort.

GESTATIONAL AGE: The majority of participants (79%) were recruited before 33 weeks of gestation, while only 21% each were recruited at 34weeks.

SYMPTOMS OF PRETERM LABOUR: The distribution of symptoms of preterm labor shows that 45% of participants reported symptoms, whereas 55% did not. Most participants (86%) had no history of preterm labor, while 14% reported such a history. Cervical length was another variable of interest, with a mean of 23.32 mm in our cohort.

Table / Figure 2: Preterm Birth (<37 weeks)

Preterm Birth	**Frequency (n)**	**Percentage (%)**
No	61	61.0
Yes	39	39.0
Total	100	100.0

Table / Figure 3: Comparison of Fetal Adrenal Gland Volume (mm3/kg)

Groups	**Mean**	**SD**	**t †**	**p value***
Term Birth	335.41	73.19	- 4.51	<0.001
Preterm Birth	397.04	80.85		

*Chi-square test †Independent t-test

The difference was statistically significant

Table / Figure 4: Comparison of Adrenal Zone Width Ratio (w/W) between the Groups

Groups	**Mean**	**SD**	**t †**	**p value***
Term Birth	48.51	2.13	-1.83	0.069
Preterm Birth	49.83	2.51		

*Chi-square test †Independent t-test

The difference was not statistically significant .

Table / Figure 5: Comparison of Adrenal Zone Depth Ratio (d/D)

Groups	Mean	SD	t †	p value*
Term Birth	51.93	1.83	1.21	0.229
Preterm Birth	51.41	2.05		

*Chi-square test †Independent t-test
The difference was not statistically significant

Table / Figure 6: Comparison of Delivery Interval (days)

Groups	Mean	SD	t †	p value*
Term Birth	29.15	10.42	9.41	<0.001
Preterm Birth	6.51	3.91		

*Chi-square test †Independent t-test
The difference was statistically significant

Table / Figure 7: Comparison of Fetal Zone Enlargement (%)

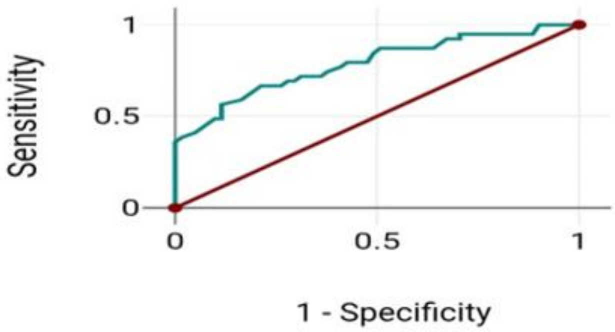
Groups	Mean	SD	t †	p value*
Term Birth	50.58	6.23	0.17	0.866
Preterm Birth	50.37	5.10		

*Chi-square test †Independent t-test.
The difference was not significant (p=0.866).

Table / Figure 8: ROC Analysis of predictive accuracy for Fetal Adrenal Gland Volume, Adrenal Zone Width Ratio and Adrenal Zone Depth Ratio

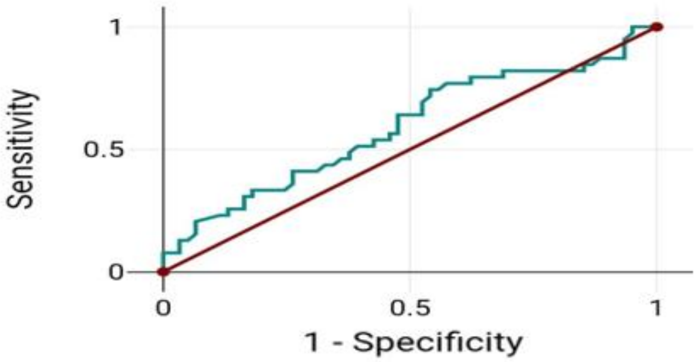
Variable	Area	95% CI Lower	95% CI Upper
Fetal Adrenal Gland Volume (mm3/kg)	0.7321	0.6231	0.8411
Adrenal Zone Width Ratio (w/W)	0.5914	0.4732	0.7096
Adrenal Zone Depth Ratio (d/D)	0.4519	0.3321	0.5717

CI = Confidence Interval



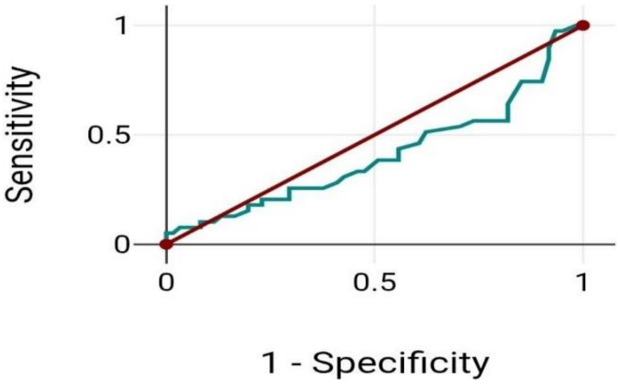
ROC Curve analysis of Foetal adrenal gland volume

Area under curve (AUC) of 0.7321 indicates **Excellent** predictive accuracy with high sensitivity and specificity .



ROC curve analysis of Fetal adrenal zone width ratio

Area under curve (AUC) of 0.5914 indicates **Moderate** prediction accuracy



ROC curve analysis of Fetal adrenal zone depth ratio

Area under curve (AUC) of 0.4519 indicates **Weak** prediction accuracy

Table / Figure 9: ROC Curve analysis of Foetal adrenal gland volume, Fetal adrenal zone width ratio and Fetal adrenal zone depth ratio in predicting preterm labour

Table / Figure 10: Sensitivity, Specificity, and Predictive Values

Statistic	Value	95% CI Lower	95% CI Upper
Sensitivity	71.79%	62.15%	81.43%
Specificity	75.41%	66.51%	84.31%
Positive Predictive Value	61.54%	51.41%	71.67%
Negative Predictive Value	82.81%	74.51%	91.11%
Prevalence	39.00%	29.44%	48.56%

CI=Confidence Interval

DISCUSSION

The association of fetal adrenal gland volume (FAGV) with preterm birth in our study highlights its predictive potential, as evidenced by a significantly higher mean volume in the preterm group compared to the term group ($p<0.001$). This finding aligns with previous studies by Turan et al. and Bhat et al., which demonstrated that an increased FAGV correlates with imminent labor, supporting the hypothesis that hormonal changes in the fetal adrenal gland trigger labor onset (12, 13, 14). Similarly, studies by Ali et al. and Gimovsky et al. noted that FAGV could differentiate between preterm and term deliveries with high specificity, further validating our results (15, 16). However, the strong sensitivity observed in our study (71.79%) suggests that FAGV should be considered alongside other markers to predict the pre term labour.

Our findings on adrenal zone width (w/W) showed moderate predictor of preterm labour with P- value 0.069 and adrenal zone depth (d/D) ratios revealed no significant difference between preterm and term births, with p-value of 0.229 respectively. These results differ from Kim et al., who reported limited utility of w/W ratios in predicting preterm labor and Eltantawy et al., who found a significant association with the depth ratio in high-risk pregnancies (17, 18). The lack of consistent findings across studies may be due to variations in sample populations and measurement techniques.

The delivery interval analysis in our study revealed significant difference between groups ($p<0.001$). This contrasts with Sharma et al., who reported similar intervals in women undergoing induction of labor but aligns with Hall's findings, where a shorter delivery interval was significantly associated with increased FAGV (19, 20). Differences in study design and population characteristics might explain these discrepancies, emphasizing the need for further research on this parameter.

Our ROC analysis revealed that FAGV had the highest area under the curve (AUC=0.7321), followed by w/W and d/D ratios. While the AUC for FAGV indicates excellent predictive accuracy, its performance was lower than reported by Sage et al. and Turan et al., who achieved higher AUC values by integrating FAGV with biochemical markers such as corticotropin-releasing hormone (21, 22). This highlights the potential for combining sonographic and biochemical tools to enhance predictive capabilities.

Fetal zone enlargement (FZE) was comparable between groups, with no significant differences ($p=0.866$). Similar findings were reported by Weiss et al., who concluded that FZE alone might not reliably predict preterm birth (9). However, combining FZE with other sonographic markers could improve its diagnostic utility.

The significant association between high FAGV and preterm birth observed in our study ($p<0.001$) aligns with Chandana et al. and Agarwal et al., who emphasized the hormonal changes within the adrenal gland as key triggers for labor (14, 7). The Cramér's V value (0.4211) suggests a meaningful association, indicating room for further investigation into additional contributing factors.

This study supports the growing evidence that FAGV is a strong predictor of preterm birth. However, its sensitivity and specificity highlight the need for combined models incorporating other biomarkers and clinical factors. Future research should focus on longitudinal studies with larger sample sizes to validate these findings and refine predictive models. Cervical length was another variable of interest, with a mean of 23.32 mm in our cohort. Shortened cervical length (<25 mm) has long been associated with preterm birth risk. Our results support the findings of Gomez et al. and Romero et al., who highlighted the role of cervical shortening as an early indicator of labor initiation (23, 11). However, integrating cervical length with FAGV may enhance predictive accuracy, as demonstrated by Goletzke et al., who combined both parameters to identify high-risk cases (8).

The integration of sonographic and biochemical tools holds promise for improving early identification and management of preterm birth, ultimately reducing its associated morbidity and mortality.

Strengths:

- The study provides valuable insights into the predictive accuracy of fetal adrenal gland volume for identifying preterm birth, using a non-invasive and widely accessible ultrasonographic technique.
- It includes a comprehensive analysis of multiple predictors, such as adrenal zone width and depth ratios, along with clinical variables like cervical length , enhancing the robustness of the findings.
- The study's cross-sectional design and sample size of 100 participants offer a sufficient dataset for initial exploration, laying the groundwork for future longitudinal studies.

Limitations:

- The cross-sectional design limits the ability to establish causal relationships between fetal adrenal gland volume and preterm birth outcomes.
- The study was conducted in a single tertiary care center, which may restrict the generalizability of the findings to other populations or healthcare settings.
- The study did not account for potential confounding factors, such as maternal stress levels or nutritional status, which could influence adrenal gland development and preterm labor outcomes.

CONCLUSION

This study highlights the potential of fetal adrenal gland volume as a reliable predictor of preterm labor, with significant differences observed between preterm and term birth groups. The ROC analysis supports its utility, showing an excellent predictive accuracy. These findings suggest that fetal adrenal gland measurements, along with other markers such as cervical length, cervicovaginal fibronectin, can aid in early risk assessment and clinical decision-making for preterm births. Implementing routine fetal adrenal gland volume measurement in high-risk pregnancies could improve early detection and management of preterm labor, reducing adverse neonatal outcomes. Further large-scale studies and the integration of these findings into clinical guidelines could enhance obstetric care and contribute to better maternal and neonatal health outcomes.

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