

# Fetal Adrenal Gland Volume – A Novel Predictor of Preterm Labor

G.B. Madhavi<sup>1</sup>, P. Sneha<sup>2</sup>

## ABSTRACT

**Introduction:** Preterm birth is a major public health problem with lasting family and societal repercussions. The etiology of most preterm births is multifactorial, with many pathological-physiological pathways being involved, such as excessive stretching, oxidative stress, decidual hemorrhage, and infection. Study aimed to find out whether the ultrasound measurement of the fetal adrenal gland remote from delivery in asymptomatic women can accurately predict spontaneous preterm birth.

**Material and methods:** 50 pregnant women with threatened preterm labour and 50 pregnant women who had term delivery, who presented to the department of Obstetrics and gynaecology at Chalmeda Anand Rao institute of Medical Sciences, Karimnagar from the period of June 2020 – June 2021 were studied prospectively. All these subjects underwent 2D Ultra sonographic measurement of adrenal gland (length, width, depth) and Fetal adrenal gland Volume is calculated by using formula  $(0.523 \times \text{Length} \times \text{Width} \times \text{Depth})$  and corrected fetal adrenal gland volume (cFAGV) was obtained by dividing Fetal Adrenal Gland Volume by the Estimated Fetal Weight, to make it a gestational age independent factor. Corrected fetal adrenal gland volume [cFAGV] of both the groups were then compared.

**Results:** Women with features of preterm labor, had a significantly high cFAGV ( $400.20 \text{ mm}^3 / \text{kg}$  body weight) in the first scan compared to those who reached term asymptotically ( $238.12 \text{ mm}^3 / \text{kg}$  body). We found a cFAGV cutoff value of  $272.18 \text{ mm}^3 / \text{kg}$  body weight and 92% sensitivity and 82.10% specificity in predicting women who are at risk of developing features of preterm labor. Of all parameters, Fetal adrenal gland width ratio had the best efficacy (sensitivity 97.87%, specificity 87.12%) followed by cFAGV (sensitivity 97.82%, specificity 83%).

**Conclusion:** Fetal adrenal gland parameters using 2D ultrasound can be used as a marker for prediction of preterm delivery. Corrected fetal adrenal gland volume [cFAGV] at term can also be used to predict the possibility of spontaneous onset of labor.

**Keywords:** Preterm, Corrected Fetal Gland Volume [cFAGV], Fetal Adrenal Zone Parameters, Spontaneous Delivery, Induced Labor

## INTRODUCTION

Preterm labor is still a concerning public health problem in obstetrics, in developing countries it still remains as a major cause of perinatal morbidity and mortality, despite tremendous research effort we still lack accurate predictors of preterm birth<sup>1</sup>.

The etiology of most preterm births is esoteric, implications of multiple mechanisms suggested that fetus may be in

control by activation its own hypothalamic- pituitary-adrenal axis at the time of birth. It also states that placental corticotrophin-releasing hormone [CRH] promotes activation of the fetal hypothalamic-pituitary-adrenal axis, which in turn stimulates the production of cortisol by the fetal adrenal gland, followed by activation of a cascade of events that suppress the mechanisms responsible for uterine quiescence.<sup>4</sup> Hence “Placental clock” plays an important role in interrupting the uterine quiescence and thus initiating a cascading of events leading to onset of labour<sup>5,6</sup>.

This information signifies that the measurement of fetal adrenal gland can be used as a noninvasive marker for onset of labour in pregnancy and has been found to be useful in prediction of preterm labour<sup>7,8</sup>. The use of volume of fetal adrenal gland as a marker of disease and in development of new strategies for the prediction of preterm birth has previously not been investigated<sup>9</sup>.

On observation, it is seen that the size of fetal adrenal gland increases in preterm birth complicated pregnancies, which makes it more likely that in the process of premature parturition fetus is an active participant. We assume that measuring the volume of adrenal gland predicts preterm and term labor with same efficacy as the concluding mechanism. Study aimed to analyse whether ultrasound measurement of the fetal adrenal gland. Remote from delivery in asymptomatic women can accurately predict spontaneous preterm birth.

## MATERIAL AND METHODS

A prospective cohort study including 50 pregnant women with threatened preterm labour and 50 pregnant women who had term delivery who presented to the department of Obstetrics and gynaecology at Chalmeda anand rao institute of medical sciences, Karimnagar from the period of June 2020 – June 2021 were included in the study. with the ethical guidelines of institutional review board the project was followed and was approved by ethical committee (Chalmeda Anand Rao Institute of Medical Sciences).

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### Inclusion criteria

All pregnant women who attended to Gynaecology and Obstetrics OPD at Chalmeda Anand Rao Institute of Medical Sciences from 28 weeks of gestation and where were planning to come for follow-up and delivery were recruited and consent was taken and categorized into Group A and Group B.

Group A includes Women with singleton fetus less than 37 weeks of gestation diagnosed to have threatened preterm labor according to ACOG [2013]; presence of uterine contraction (at least 4 in 20min or 8 in 60min ), cervical effacement <80% cervical dilatation <1cm<sup>11</sup>.

Group B includes women who continued their pregnancy till term and delivered at term i.e., after 37 weeks of gestation.

### Exclusion criteria

- \*Suspected fetal growth restriction (sonographic fetal weight less than 10<sup>th</sup> percentile for gestational age)
- \*Maternal medical complications (Hypertension , Pre-eclampsia , Diabetes ,Thyroid or Adrenal diseases)
- \*Presence of fetal heart rate abnormalities at enrollment (bradycardia or prolonged variable decelerations)
- \*Preterm PROM
- \*Placenta previa
- \*Lower urinary tract infection or genital infection
- \*Fetal congenital anomaly

Study information sheet were provided to all participants, questions regarding their study and participation were allowed to ask. Their written informed consent was taken. Demographic details, education, residence, occupation, consanguinity , genital age , height, weight , history of drug usage and occupation education, special habits of her husband ,obstetric history, examination findings, and investigation results of women enrolled were recorded in a standard proforma. Determination of gestational age was done according to their last menstrual period or early first trimester SEDD. All women, who gave consent to participate in the study, were subjected to 2D ultrasonographic measurement of length, width and depth of adrenal gland and the corrected fetal adrenal gland volume (cFAGV) was calculated and fetal adrenal zone parameters including the width ratio and depth ratio were taken at 28–34 weeks. These women also

underwent a transvaginal(TVS) ultrasonographic cervical length (CL) measurement. Till term the cohort was followed up, and between 37 and 39 weeks parameters of cFAGV and fetal adrenal zone were reassessed and repeated. At the time of presentation to measure cFAGV and fetal adrenal zone parameters the women with signs and symptoms of preterm labour (<37 completed weeks) underwent ultrasonographic scan.

Details of ultrasonographic imaging used for all cases were: Philips affinity 70G Ultrasound Machine (manufactured in USA). all participants were imaged by a single sonographer to avoid bias.

To take measurements, the right fetal adrenal gland was imaged, as it is better visualized, than left fetal adrenal gland which obscured by the rib shadow. Above the kidneys the fetal adrenal gland appears as inverted V Shaped structure/cap like structure . Both sagittal and transverse planes were obtained. The length of the gland, width and depth of the adrenal gland were measured in the sagittal plane and transverse plane respectively. Using the ellipsoid formula ( $0.523 \times \text{length} \times \text{width} \times \text{depth}$ ) fetal adrenal gland volume was calculated. To make cFAGV a gestational age independent factor it was obtained by dividing fetal adrenal gland volume with estimated fetal weight. Standard criteria were followed to measure cervical length. Closed portion of the cervix from the internal to external os was measured with a transvaginal probe (5-9MHz).

### RESULTS

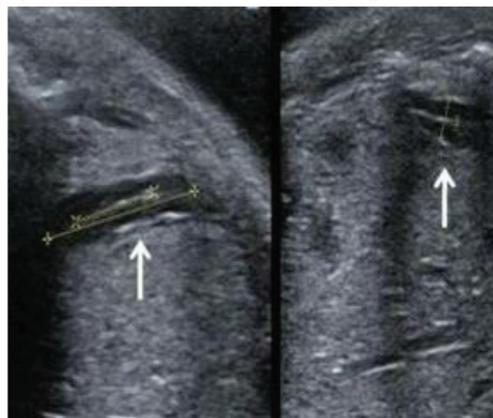
100 pregnant women were enrolled in study at 28-34 weeks of gestation, 50 women reached term without complication, 50 women presented with features of preterm labor. All the study population were presented with features of preterm labor and all were in active labor and delivered before any intervention.

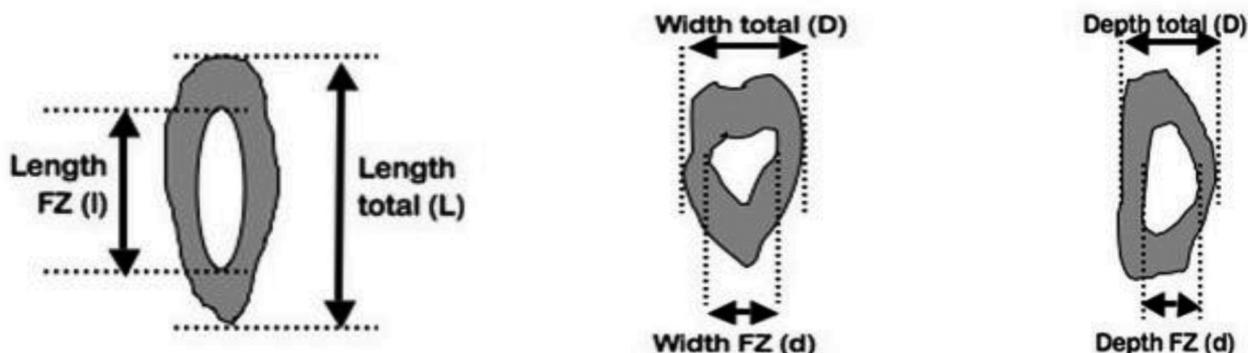
Mean age of the study population was 27.12 +/- 3.0 years, mean age of control population was 26.9 +/- 2.6. Most of them are primigravidas [80%], 10 women among the study population had previous history of preterm delivery with a mean gestational age at preterm delivery in previous pregnancy being 32.12 +/- 1.52 weeks. Six of these had a preterm delivery even in present pregnancy. In the study

A) sagittal section of fetal adrenal gland



B) transverse section fetal adrenal gland





| Variables  | Group A (N=50) | group B (N=50) |
|--|----------------|----------------|
| Mean age   | 27.12 +/- 3.0  | 26.9 +/- 2.6   |
| Mean period of Gestation (weeks)                               | 34.3 +/- 1.01  | 39.1 +/- 1.05  |
| Primigravida   | 80%(N=40)      | 80%(N=40)      |
| Multigravida   | 20%(N=10)      | 20%(N=10)      |
| History of preterm in previous pregnancy                       | 10             | 0              |
| History of preterm labor who had preterm in current pregnancy. | 6              | 0              |

**Table-1:** Demographic parameters of study participants

| cFAGV (mm <sup>3</sup> /kg b.wt) | Group A (N=50) | Group B (N=50) |
|----------------------------------|----------------|----------------|
| >400.20                          | 32 (64%)       | 0 (0%)         |
| 400.20 – 346                     | 15 (30%)       | 1 (2%)         |
| 346 – 272                        | 2 (4%)         | 3 (6%)         |
| 272 – 238                        | 1 (2%)         | 18 (36%)       |
| <238                             | 0 (0%)         | 28 (56%)       |

**Table-2:** Comparison of cfagv values in both groups

| Statistical Characteristics | cFAGV(%) | Fetal adrenal gland width ratio (%) | Cervical length (%) |
|-----------------------------|----------|-------------------------------------|---------------------|
| Sensitivity                 | 97.82%   | 97.87%                              | 56.67%              |
| Specificity                 | 83%      | 87.12%                              | 90.8 %              |

cFAGV - corrected Fetal Adrenal Gland Volume, FAZ - Fetal Adrenal Zone, FAG Fetal Adrenal Gland

**Table-4:** Comparison of the efficacy of various parameters (with the ROC determined cutoff values) and cervical length (B 2.5 cm) during first scan in prediction of preterm delivery

| Variable                                | Group B (N = 50) | Group A (N=50) |
|---|------------------|----------------|
| cFAGV (mm <sup>3</sup> /kg body weight) | 238.12           | 400.20         |
| FAZ/FAG width ratio                     | 0.48             | 0.55           |
| FAZ/FAG depth ratio                     | 0.46             | 0.49           |
| Cervical length (cm)                    | 3.4              | 2.8            |

**Table-3:** Comparison of fetal adrenal gland parameters and cervical length measurements in both groups

| Parameters                    | Group-A (N=50) | Group-B (N=50) |
|-------------------------------|----------------|----------------|
| Low APGAR score               | 22(44%)        | 5(10%)         |
| NICU admission                | 30(60%)        | 4(8%)          |
| Low birth weight              | 36(72%)        | 0              |
| Respiratory distress syndrome | 18(36%)        | 6(12%)         |
| Sepsis                        | 3(6%)          | 0              |
| Mortality                     | 0              | 0              |

**Table-5:** The perinatal outcome in both groups

population the mean period of gestation of preterm delivery was 34.3+/-1.01weeks.

Table 2 shows that in our study maximum number of patients in group A have corrected Fetal adrenal gland volume of >400.20 mm<sup>3</sup>/kg b.wt and maximum number of patients in Group B have cFAGV value of <238 mm<sup>3</sup>/kg b.wt. No patients of Group B have corrected Fetal adrenal gland volume of >400.20 mm<sup>3</sup>/kg b.wt and No patients of Group A have corrected Fetal adrenal gland volume of <238 mm<sup>3</sup>/kg b.wt .

During the first plotting a ROC to determine the cutoff value of cFAGV ,area under the curve was 0.90 with 95% confidence interval of lower limit of 0.83 and upper limit of 0.97. A cutoff value of 272 mm<sup>3</sup>/kg body weight showed 90% sensitivity and 81.9% specificity have been found in predicting women who are at risk of developing features of

preterm labor based on the first scan done between 28 and 34 weeks. However, for preterm delivery, a cutoff value of 346 mm<sup>3</sup>/kg body weight had a 96.7% sensitivity and 83% specificity in our study population.

In Table 3, On comparing the parameters of adrenal gland and cervical length during the first scan between those who uneventfully progressed to term and those who presented with the suggestive features of preterm labor. Eventually the women who developed the preterm labor features had a high cFAGV (400.20mm<sup>3</sup>/kg body weight)compared to those who reached term asymptotically (238.12mm<sup>3</sup>/kg body weight).

A cutoff value of 272 mm<sup>3</sup> /kg body weight showed 90%

sensitivity and 81.9% specificity in predicting women who are at risk of developing features of preterm labor based on the first scan done between 28 and 34 weeks. On comparison of fetal adrenal gland parameters, in the study population statistically significant difference was found between women who had a preterm delivery and those who progressed till term. Among those participants the preterm delivered were having significantly less cervical length. To determine the cutoff values ROC was plotted. Depending on these values determined by the ROC for cFAGV (cutoff 346.28 mm<sup>3</sup>/kg body weight), fetal adrenal gland width ratio (cutoff 0.71) and fetal adrenal gland depth ratio (cutoff 0.59) and efficacy in terms of sensitivity, specificity, positive and negative predictive values were calculated. This was compared with the efficacy of cervical length (with a standard cutoff of 2.5 cm) for prediction of preterm delivery.

In the study population significant difference between women who had a preterm delivery and those who progressed till term was statistically found. On observation Cervical length also was significantly less among those who eventually delivered preterm.

Table 4 Comparison of the efficacy of various parameters (with the ROC determined cutoff values) and cervical length (B 2.5 cm) during first scan in prediction of preterm delivery. Comparison of the cervical length (B 2.5 cm) and efficacy of various parameters during first scan in prediction of preterm delivery. Fetal adrenal gland width ratio had the best efficacy (sensitivity 97.87%, specificity 87.12%) followed by cFAGV (sensitivity 97.82%, specificity 83%)

group A women delivered neonates of low APGAR score with 44% requiring NICU admission 60%, with low birth weight (LBW) of 72% and showing respiratory distress syndrome (36%) and sepsis 6%.

group B women delivered neonates of low APGAR score with 10% requiring NICU admission 8%, and showing respiratory distress syndrome (12%).

## DISCUSSION

On the concept of placental clock the idea of fetal adrenal gland parameters to predict the onset of labor is based. Some studies in the past validate the idea for prediction of [1

Chandana S. Bhat et al. have found a cFAGV cutoff value of 271.16 mm<sup>3</sup>/kg body weight and 90% sensitivity and 81.9% specificity in predicting women who are at risk of developing features of preterm labor based on the scan done between 28 and 34 weeks. However, for preterm delivery, a cutoff value of 348.78 mm<sup>3</sup>/kg body weight had a 96.7% sensitivity and 83% specificity in study population<sup>1</sup>.

Turan et al. were more specific and concluded that a cFAGV of greater than 422 mm<sup>3</sup>/kg was best in predicting preterm birth within 5 days, with a sensitivity and specificity of 92% and 99%, respectively. Multiple logistic regression analysis showed that cFAGV was the only significant independent predictor factor of preterm birth within 5 days of measurement<sup>7,8</sup>.

We found a cFAGV cutoff value of 272.18 mm<sup>3</sup>/kg body weight showed 92% sensitivity and 82.10% specificity in

predicting women who are at risk of developing features of preterm labor based on the scan done between 28 and 34 weeks. However, for preterm delivery, a cutoff value of 346.28 mm<sup>3</sup>/kg body weight had a 95.87% sensitivity and 83.2% specificity in our study population.

2D ultrasound might help to correlate findings as per period of gestation as early as 15<sup>th</sup> week of gestation. cFAGV increases with the risk of preterm delivery and can be used to assess the risk of preterm delivery and followup. Till now only the cFAGV has been emphasized upon in the literature; however, we found that fetal adrenal gland width ratio had the best efficacy (sensitivity 96.67%, specificity 86.2%) in prediction of preterm delivery.

2D and 3D ultrasound studies have concluded that with 3D ultrasound estimation of fetal adrenal gland volume is more accurate. Investigators of the same also have described that enlargement on 2D ultrasound is better predictor of preterm labor than 3D volume calculation.

We also observed association of probability of spontaneous onset of labor with parameters of fetal adrenal gland. With the results of other studies our findings are in agreement, that shows activation of fetal hypothalamic pituitary adrenal axis in primates and humans results in increased output of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione and cortisol both at term or preterm. If studied in a large number of population with variables results will be more beneficial. Day-wise predictable cutoffs definitely will give a new position to the fetal adrenal glands in the prediction of labor (preterm or term) in modern obstetrics. Predictability of this kind will provide the obstetrician time to utilize the resources and will give clarity about the plan to parturient and her family.

## CONCLUSION

Measurement of fetal adrenal gland parameters by 2D ultrasound can be taken as a marker for preterm delivery prediction. To predict the possibility of spontaneous onset of labor at term corrected fetal adrenal gland volume (cFAGV) can also be used.

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