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ORIGINAL ARTICLE

Fetal Adrenal Gland Volume a Novel Predictor of Onset of Labor

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Abstract

Introduction There is a definite need to find a highly sensitive and specific, noninvasive, and cost-effective marker for prediction of preterm labor. We hypothesize that a measurement of adrenal gland volume can predict a preterm as well as a term labor.

Materials and Methods Two hundred and sixty-eight pregnant women were enrolled in the study at 28–34 weeks' antenatal visit. Final analysis was done in 204. All of them were subjected to 2D ultrasonographic measurement of the corrected fetal adrenal gland volume (cFAGV) and fetal adrenal zone parameters including the width ratio and depth ratio. The cohort was followed up to term, and a reassessment of cFAGV and fetal adrenal zone parameters was repeated between 37 and 39 weeks. Women who presented with features of preterm labor had a scan at the time of presentation to record cFAGV and fetal adrenal zone parameters.

Results Women, who developed features of preterm labor eventually, had a significantly high cFAGV (404.70 mm^3/kg body weight) during the first scan compared to those who reached term asymptomatically (241.35 mm^3/kg body

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weight). A cutoff value of 271.16 mm^3/kg body weight showed 90% sensitivity and 81.9% specificity. Fetal adrenal gland width ratio had the best efficacy (sensitivity 96.67%, specificity 86.2%) followed by cFAGV (sensitivity 96.67%, specificity 83%) for predicting preterm delivery.

Conclusion 2D ultrasound measurement of fetal adrenal gland parameters can be used as a marker for prediction of preterm delivery. cFAGV at term can also be used to predict the possibility of spontaneous onset of labor.

Keywords Preterm · Corrected fetal adrenal gland volume (cFAGV) · Fetal adrenal zone parameters · Spontaneous delivery · Induced labor

Introduction

'Placental clock' plays a pivotal role in interrupting the uterine quiescence and thus initiating a cascade of events leading to onset of labor [1, 2]. The placental clock works through its mediator placental corticotrophin-releasing hormone (CRH), which in turn causes activation (and enlargement) of the fetal adrenal gland. This knowledge imparts a clue that fetal adrenal gland measurement in pregnancy can be used as a noninvasive marker for onset of labor. This concept has been investigated and found useful in prediction of preterm labor [3, 4].

As the psychosocial structure of the society is changing, we find increasing number of women who are interested in prediction of spontaneous onset of labor, even at term. In the present scenario, a clinical cervical assessment or an ultasonographic cervical length measurement is used for the same. We hypothesize that a measurement of adrenal gland volume can predict a preterm as well as a term labor with same efficacy as the final mechanism and 'placental clock' theory holds good for both.

Materials and Methods

This prospective observational study was conducted at a tertiary care center affiliated to a medical university, over a period of 2 years (September 2013–August 2015). The project followed ethical guidelines of the institutional review board and was approved by Ethics Committee, Kasturba Hospital Manipal, Karnataka, India, (IEC 389/2013).

Women with uncomplicated singleton pregnancy who presented in our antenatal clinic between 28 and 34 weeks of gestation and were planning to come for follow-up and delivery were recruited. Cases with any medical or obstetric complication were excluded. All participants were provided with a study information sheet, and they were allowed to ask questions regarding the study and their participation. A written informed consent was then obtained.

Demographic details, obstetric history, examination findings, and investigation results of women enrolled were recorded in a standard pro forma. Gestational age was determined according to the last menstrual period, when it agreed with first trimester ultrasound examination. Otherwise, only the later was considered for the same.

All women, who consented to participate in the study, were subjected to 2D ultrasonographic measurement of the corrected fetal adrenal gland volume (cFAGV) and fetal adrenal zone parameters including the width ratio and depth ratio at 28–34 weeks. Additionally, these women also underwent a transvaginal ultrasonographic cervical length (CL) measurement. The cohort was followed up to term, and a reassessment of cFAGV and fetal adrenal zone parameters was repeated between 37 and 39 weeks. Women who presented with features of preterm labor (before 37 completed weeks) underwent a scan at the time of presentation to record cFAGV and fetal adrenal zone parameters.

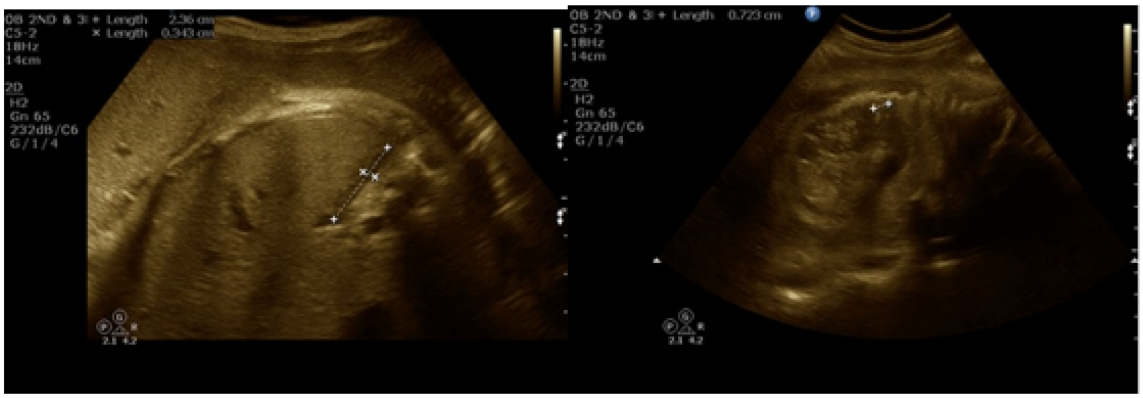
Details of ultrasonographic imaging used for all cases were: Philips HD 11 XE, 2 D Ultrasound Machine (manufactured in USA), model number 989605325131. To avoid the bias, all patients were imaged by a single sonographer.

To obtain measurements, the right fetal adrenal gland was imaged, as it is better visualized, compared to left adrenal gland which is usually obscured by the rib shadow. The fetal adrenal gland is visualized as a hypoechoic, inverted 'V'-shaped structure/cap-like structure above kidney. Both transverse and sagittal planes were obtained. The length of the gland was measured in the sagittal plane, whereas the width and depth of the adrenal gland were measured in the transverse plane (Fig. 1a, b).

The fetal adrenal zone is visualized as hyperechoic center in the fetal adrenal gland. The width and depth of the fetal adrenal zone were noted in the transverse plane (Fig. 1).

The fetal adrenal gland volume was calculated using the ellipsoid formula ($0.523 \times \text{length} \times \text{width} \times \text{depth}$). Corrected fetal adrenal gland volume (cFAGV) was obtained from dividing fetal adrenal gland volume by the estimated fetal weight, so as to make it a gestational-age-independent factor.

To measure the cervical length, standard criteria were followed. A transvaginal probe (5–9 MHz) was used, and closed portion of the cervix from the internal to external os was measured.



(a) (b)

Fig. 1 Right fetal adrenal gland width and depth in transverse section (**a**), right fetal adrenal gland length in sagittal section (**b**), right fetal adrenal zone width and depth in transverse section

Statistical Analysis

Data collection, computation, and analysis were done using SPSS 16 software. Demographic details were expressed as means. cFAGV, fetal adrenal zone parameters, and the cervical length were expressed as medians. Mann–Whitney U test and Wilcoxon signed-rank test were used to compare the medians. Significance was assumed at a p value of less than 0.05. Receiver operated curve (ROC) was plotted to determine the cutoff values, and the sensitivity and specificity were noted and area under the curve of 0.9–1: excellent predictor, 0.8–0.9: good predictor, 0.7–0.8: fair predictor, 0.6–0.7: poor predictor, 0.5–0.6 fails to predict, were assumed.

Results

Two hundred and sixty-eight pregnant women were enrolled in the study at 28–34 weeks' antenatal visit. During the follow-up period, 53 women had to be excluded as they developed gestational hypertension or preeclampsia (28), gestational diabetes (13), intrauterine growth restriction (5), preterm pre-labor rupture of membranes (3), placenta praevia (2), and severe upper respiratory tract infection (2). Eleven women were lost to follow-up. Thus, a total of 204 women were included in the final analysis study. Out of these, 138 women reached term without any complication, whereas 66 (32.35%) presented with features of preterm labor. Among those who presented with preterm labor, only 30 women (14.7% of total cohort studied) delivered preterm, while 36 women among this group also progressed to term. Thus a total of 174 women progressed till term (Fig. 2). Among 66 of the study population was presented with features of preterm labor, 20 were in active labor who delivered before any intervention. Rest 46 received tocolytics with tablet nifedipine 20 mg stat followed by 10 mg TDS for average duration of 2 days.

Mean age of the study population was 27.20 ± 3.72 years. Most of them were primigravidas (74%). Eight women among the study population had a previous history of preterm delivery with a mean gestational age at preterm delivery in the previous pregnancy being 31.52 ± 1.41 weeks. Seven of these had a preterm delivery even in the present pregnancy.

Women who were enrolled for the study underwent their first scan at a mean gestational age of 32.27 ± 1.25 weeks. Women presented with features of preterm labor within a mean duration of 8.16 ± 1.30 days from the time of first scan at a mean period of gestation of 33.35 ± 1.32 weeks. The mean period of gestation of preterm delivery in the study population was 34.30 ± 1.01 weeks. Mean period of gestation at the follow-up scan of at term was 38.30 ± 1.01 weeks. There was an interval of 5.21 ± 0.67 days between this scan and delivery with a mean gestational age at delivery of 39.10 ± 1.05 weeks.

We compared the adrenal gland parameters and cervical length during the first scan (28–34 weeks) among those who progressed uneventfully to term with those who presented with features suggestive of preterm labor (Table 1). Women, who developed features of preterm labor eventually, had a significantly high cFAGV (404.70 mm^3/kg body weight) during the first scan compared to those who reached term asymptomatically (241.35 mm^3/kg body weight). The difference in the fetal adrenal zone ratios and the cervical length were not statistically significant to determine those at risk of developing features of preterm labor.

On plotting a ROC to determine the cutoff value of cFAGV, during the first scan, area under the curve was

Fig. 2 Consort statement

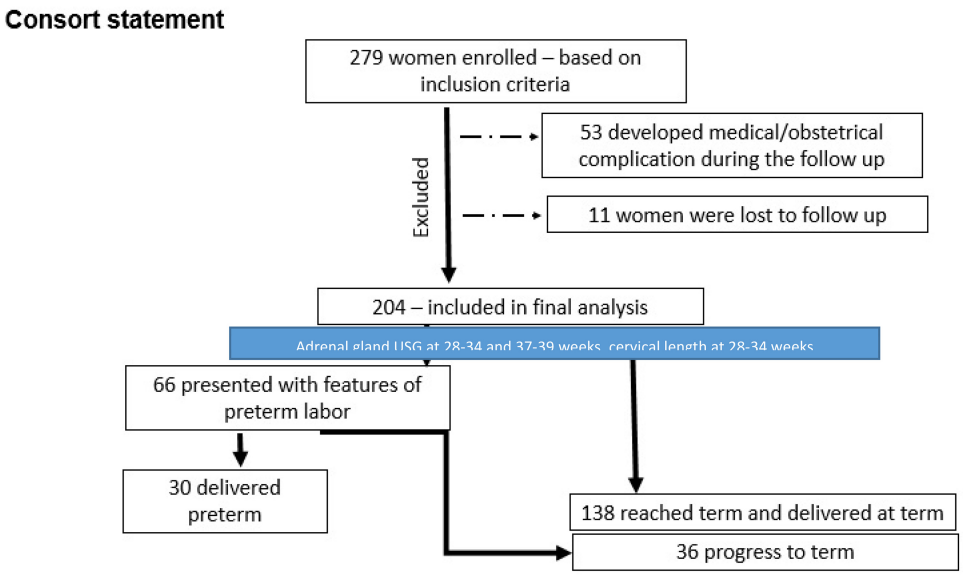


Table 1 Comparison of fetal adrenal gland parameters and cervical length measurements during the first scan done between 28 and 34 weeks, among women who continued till term versus women who eventually presented with features of preterm labor

Variable	Women who continued till term (N = 138)	Women who eventually presented with features of preterm labor (N = 66)	p value
cFAGV (mm^3/kg body weight)	241.35	404.70	0.00
FAZ/FAG width ratio	0.48	0.55	0.06
FAZ/FAG depth ratio	0.46	0.49	0.53
Cervical length (cms)	3.4	3.1	0.6

cFAGV corrected fetal adrenal gland volume, *FAZ* fetal adrenal zone, *FAG* fetal adrenal gland)

0.90 with 95% confidence interval of lower limit of 0.83 and upper limit of 0.97. A cutoff value of 271.16 mm^3/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 (Fig. 2).

On comparing fetal adrenal gland parameters, we found a statistically significant difference between women who had a preterm delivery and those who progressed till term in the study population. Cervical length also was significantly less among those who eventually delivered preterm. (Table 2) ROC was hence plotted to determine the cutoff values. Based on these cutoff values determined by the ROC for cFAGV (cutoff 348.78 mm^3/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. Fetal adrenal gland width ratio had the best efficacy (sensitivity 96.67%, specificity 86.2%) followed by cFAGV (sensitivity 96.67%, specificity 83%) (Table 3).

Table 2 Comparison of fetal adrenal gland parameters and cervical length measurements during the first scan done between 28 and 34 weeks, among women who continued till term versus women who eventually delivered preterm

Variable	Women who continued till term (N = 138)	Women who delivered preterm (N = 30)	p value
cFAGV (mm^3/kg body weight)	241.35	422.34	0.00
FAZ/FAG width ratio	0.48	0.62	0.00
FAZ/FAG depth ratio	0.46	0.55	0.02
Cervical length (cm)	3.4	2.5	0.02

cFAGV corrected fetal adrenal gland volume, *FAZ* fetal adrenal zone, *FAG* fetal adrenal gland)

Table 3 Comparison of the efficacy of various parameters (with the ROC determined cutoff values) and cervical length (≤ 2.5 cm) during first scan in prediction of preterm delivery

Statistical Characteristics	*c* FAGV (%)	Fetal adrenal gland width ratio (%)	Fetal adrenal gland depth ratio (%)	Cervical length (%)
Sensitivity	96.67	96.67	80	56.67
Specificity	83	86.2	54	90.8
Positive predictive value	49.50	54.69	23.05	51.52
Negative predictive value	99.31	99.33	94.00	92.40

cFAGV corrected fetal adrenal gland volume, *FAZ* fetal adrenal zone, *FAG* fetal adrenal gland)

Table 4 Distribution of the fetal adrenal gland parameters estimated during the second scan of women who went into spontaneous labor at term and those who had to be induced ($N = 174$)

Variable	Women who went into spontaneous labor ($N = 117$)	Women who had to be induced ($N = 57$)	*p* value
Corrected fetal adrenal gland volume (mm^3/kg body weight)	393.05	290.92	0.01
FAZ/FAG width ratio	0.70	0.67	0.52
FAZ/FAG depth ratio	0.65	0.61	0.5

cFAGV corrected fetal adrenal gland volume, *FAZ* fetal adrenal zone, *FAG* fetal adrenal gland)

In this study, we went one step further ahead to study adrenal parameters among the two groups of the women who reached term (those who delivered spontaneously versus those who had to be induced in view of past dates) (Table 4). We found a statistically significant difference in the cFAGV among these two group at the scan which was done at term (spontaneous labor 393.05 mm^3/kg versus induced labor 290.92 mm^3/kg; *p* value 0.01).

Discussion

The idea of using fetal adrenal gland parameters to predict the onset of labor is based on the concept of 'placental clock.' There have been some studies in the past to validate this idea for prediction of preterm delivery [3, 4]. Identification of the process of parturition that occurs over weeks to months prior to delivery timeline may provide an opportunity to clinical intervention [5, 6].

We found a cFAGV cutoff value of 271.16 mm^3/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^3/kg body weight had a 96.7% sensitivity and 83% specificity in our study population. Turan et al. were more specific and concluded that a cFAGV of greater than 422 mm^3/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 cAFGV was the only significant independent predictor factor of preterm birth within 5 days of measurement [3, 4]. Reference range of fetal adrenal gland measurements using 2D ultrasound have been developed, starting from as early as 15th week of pregnancy, which might help to correlate findings as per the period of gestation. [7] It is very obvious that the cFAGV increases with the risk of preterm delivery and can be relied upon to predict and follow-up women for assessing the risk of preterm delivery. 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.

Studies comparing 2D and 3D ultrasounds have concluded that estimation of fetal adrenal gland volume is more accurate for prediction of preterm labor with 3D ultrasound. [4] Same investigators have also demonstrated that enlargement in depth of fetal zone by 2D ultrasound is even better predictor of preterm labor than 3D volume calculation. [3].

Additionally, we also observed an association of fetal adrenal gland parameters with the probability of spontaneous onset of labor at term. Our findings are in agreement with the results of other studies, which showed that, in primates and humans, activation of the fetal hypothalamic–pituitary–adrenal axis results in increased output of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, and cortisol, both at term or preterm [8].

Specific measurements and cutoff values can be analyzed in future to make it more applicable for prediction on onset of labor even at term. In the literature, not only for prediction of labor but fetal adrenal gland measurements have also been used to evaluate successful outcome of induction of labor [9].

The results will be more beneficial if studied in a larger population and with variables. Establishment of day-wise predictable cutoffs will definitely give fetal adrenal glands a new position in the prediction of labor (term or preterm) in modern obstetrics. This kind of predictability not only will give the obstetrician time to optimally utilize resources but also will give the parturient and her family a clarity of plan.

Conclusion

2D ultrasound measurement of fetal adrenal gland parameters (fetal adrenal gland width ratio and cFAGV) can be used as a marker for prediction of preterm delivery. cFAGV at term can also be used to predict the possibility of spontaneous onset of labor.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Rights This research involved no human participants and/or animals.

Informed Consent Informed consent was obtained from all the patients in the study.

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