

## FETAL ADRENAL GLAND BIOMETRY: A POTENTIAL PREDICTOR OF PRETERM BIRTH

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### Abstract

**Background:** Preterm birth is an important challenge in obstetrics and contemporary perinatology in India. Timely recognition, intervention and appropriate management is integral in curbing the upsurge in its incidence and consequent poor perinatal outcome. This study was conducted taking into account the potential mechanism of preterm labor: premature activation of the placental-adrenal endocrine axis wherein elevation of maternal cortisol leads to an increased production of placental corticotrophin releasing hormone which causes an increase in dehydroepiandrosterone produced by the fetal zone of the adrenal gland and its enlargement. This activates a cascade leading to early loss of uterine quiescence, consequently causing cervical modelling, ripening and preterm birth.

**Aim and Objectives:** To assess fetal adrenal gland volume and fetal zone enlargement on ultrasound and evaluate its efficacy in the prediction of preterm birth.

**Methods:** This was a hospital based prospective study in which pregnant women with an uncomplicated live singleton pregnancy between 28 to 34 weeks of gestation were subjected to obstetric ultrasonography wherein fetal adrenal gland volume and fetal zone enlargement was measured. They were then followed up until their delivery, whether term or preterm and its correlation with fetal adrenal gland parameters was assessed.

**Result:** Corrected fetal adrenal gland volume showed the highest sensitivity of 90.0% and a specificity of 96.7% with a cut off value of 632.50 mm<sup>3</sup>/kg while fetal zone enlargement showed a sensitivity and specificity of 72.7% and 60.9% respectively.

**Conclusion:** This study concludes that fetal adrenal gland biometry can be used as a noninvasive, cost effective and potential new marker for the prediction of preterm birth.

### Introduction

Preterm birth is defined as the onset of delivery prior to 37 completed weeks but after the age of viability, which may range from 24 weeks to 28 weeks, based on which those born before 28 weeks are termed as extreme preterm and those above 32 weeks are late preterm<sup>1</sup>.

Preterm labor remains to be one of the most important challenges of contemporary perinatology and constitutes one of the main reasons of perinatal mortality. Every year an estimated 15 billion babies are born preterm. More than 60 percent of these preterm births occur in Asia and Africa<sup>2</sup>. Preterm birth is the leading cause of death among children less than five years of age, constituting to about one million deaths every year.

India contributes the greatest number of preterm births worldwide. Out of 27 million babies born every year in India, 3.5 million babies are born preterm<sup>2</sup>. Out of these, almost three fourths of mortalities could be prevented by cost-effective interventions. Due to the upsurge in the incidence of preterm labor and increased annual cost in the care of preterm infants, there is a definite need to find a highly sensitive and specific, noninvasive, cost effective and quantitative marker for the prediction of preterm labor

for its timely management to reduce the consequent neonatal morbidity and mortality. The potential mechanism for preterm births is the premature activation of the placental-adrenal endocrine axis. Elevation of maternal cortisol activates this axis, yielding the increased production of placental corticotrophin releasing hormone. This causes an increase in dehydroepiandrosterone produced by the fetal zone of the adrenal gland. This activates a cascade leading to an early loss of uterine quiescence. The end result of this pathway is cervical modelling and ripening. Due to this physiological chain of events, there is a consequent enlargement of the fetal adrenal gland. Measurement of the fetal adrenal gland volume and the fetal zone enlargement can be used as a predictor of preterm labor. This study was performed in a tertiary care hospital in the state of Rajasthan. Rural population makes up the majority of the patients we cater to, wherein antenatal visits early in pregnancy are a rare sight. Most of these women attend the hospital in their third trimester of pregnancy for the very first time. Thus, this study aims to analyze the role of fetal adrenal gland biometry as a predictor of preterm birth in women with 28 weeks of gestation to 34 weeks of gestation attending the

antenatal clinic. This would aid in the prediction of preterm labor in women presenting late in pregnancy and effective interventions and treatment to improve the perinatal outcome. A very few studies have been done in India about the role of fetal adrenal gland biometry in preterm birth. This study aims to evaluate fetal adrenal gland biometry and consolidate the existing literature on its role in the prediction of preterm labor.

### Aims and Objectives

The aim of this study is to assess fetal adrenal gland volume and fetal zone enlargement on ultrasound and evaluate its efficacy in the prediction of preterm birth.

### Material and Methods

This was a hospital based prospective cohort study conducted in the department of Obstetrics and Gynecology in SMS Medical College, Jaipur wherein 103 pregnant women with an uncomplicated singleton live pregnancy of 28-34 weeks of gestation fulfilling the inclusion criteria and giving a written, informed consent were recruited for the study. Sample size of 120 pregnant women was taken for the present study which was calculated at 80% study power and an alpha error of 0.05, assuming an AUC of 0.569 for cervical length in predicting preterm labor and 50 % incidence of preterm labor in the cohort as per results of seed article, expecting 20% dropouts or loss to follow up or attrition. The final sample size was 103 participants as seventeen patients were lost to follow up due to the COVID 19 pandemic. Patients with an uncomplicated singleton live pregnancy with 28 to 34 weeks of gestational age, willing to participate in the study, with or without prior preterm births or abortions were included in the study. Patients having multifetal pregnancy, polyhydramnios, pregnancy with complications like antepartum hemorrhage, preeclampsia and pregnancy with medical illness like diabetes mellitus, heart disease, fetal abnormalities incompatible with life, uterine anomalies, Urinary tract infection and other bacterial infections were excluded from the study.

Gestational age was determined from the last menstrual period and a first trimester scan.

Approval from the institutional research, review board and ethical committee was taken.

Standardized data collection on a predesigned study proforma including a full antenatal workup and routine investigations was done. This included detailed history and

examination of the patient and panel of all routine investigations.

Patients were subjected to obstetric ultrasonography wherein fetal adrenal gland biometry and cervical length were assessed.

Ultrasound was done using linear array transducer of 9-11 MHz frequency and a linear obstetrics preset.

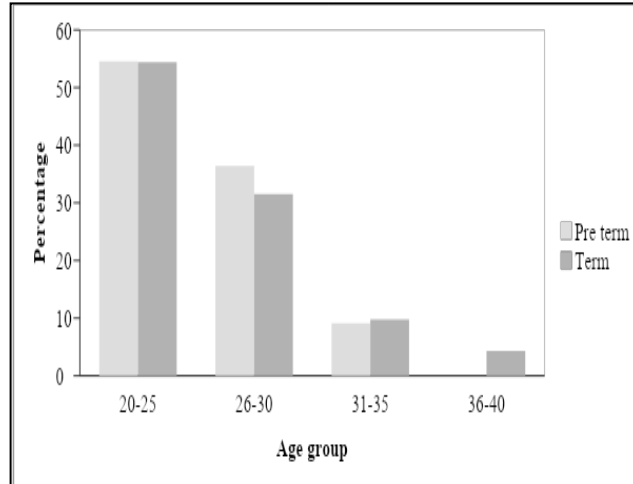
Fetal adrenals can be focussed in the axial plane, by smoothly navigating the transducer cranially above the level of kidneys. The central hyperechoic part of the fetal adrenal gland (fetal zone) is measured in the sagittal or coronal plane along with the maximum dimension of the gland in the same plane to give fetal zone depth (d) and total gland depth (D).

The d/D ratio is charted as a percentage and called as a marker of fetal zone enlargement (FZE) The total gland dimensions are taken in three orthogonal planes and gland volume is estimated using the ellipsoid formula ( $a*b*c*0.52$ ). This is further divided by the estimated fetal weight (EFW) in kilograms to yield corrected fetal adrenal gland volume (cAGV) in cubic millimeters per kilograms ( $mm^3/kg$ ). EFW is calculated automatically using Hadlock formula based on four common fetal measurements i.e. biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL).

These measurements were done on both adrenal glands however, left-sided measurements were used due to its semilunar shape. In patients with increased abdominal fat, the fetal adrenals were assessed using a 3.5 MHz curvilinear probe. All these women were followed up until delivery, whether preterm or term and its correlation with the fetal adrenal gland parameters were assessed.

### Result

The mean age of women who delivered preterm was found to be  $25.63 \pm 4.20$  years and the mean age of women who delivered at term was also found to be  $26.04 \pm 4.05$  years. 54.54 percent were lying in the age group of 20-25 in both preterm and term group. 36.36 percent in preterm group and 31.52 percent in term were lying in the age group of 26-30. 9.78 percent in preterm group and 9.09 percent in term group of 31-35 age group. 4.34 percent were found to be in age group of 36-40 in term group. On comparing it was found that age of the two groups in the study was comparable ( $p=0.99$ ).



**Figure 1: Distribution of women with respect to age**

**Table 1: Age distribution of patients**

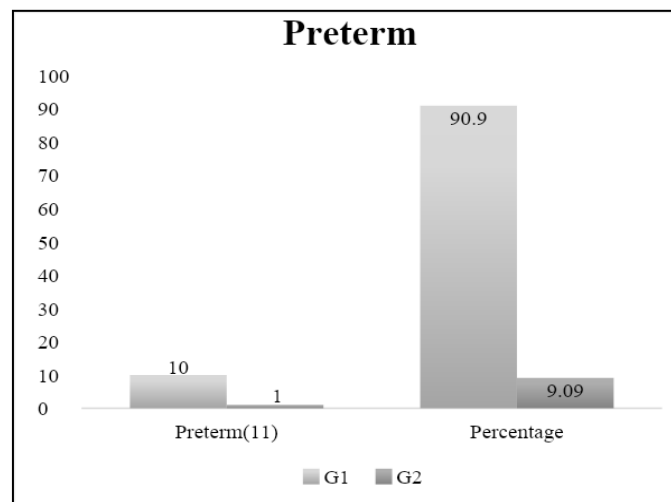
Age	Preterm(11)	Percentage	Term(92)	Percentage	P value
20-25	6	54.54	50	54.35	0.99
26-30	4	36.36	29	31.52	
31-35	1	9.09	9	9.78	
36-40	0	0	4	4.34	
<b>Total</b>	<b>11</b>	<b>100</b>	<b>92</b>	<b>100</b>	

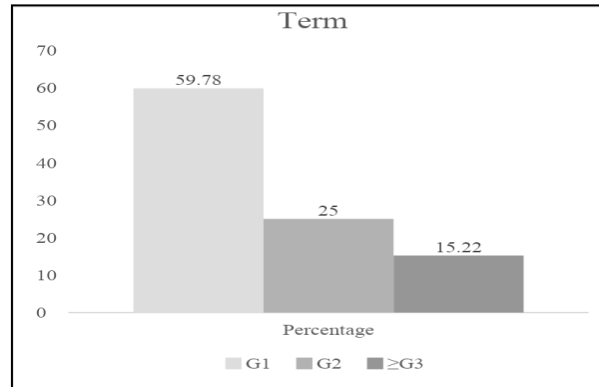
This table concludes that out of 11 patients who delivered preterm, 10 were primigravida while only one patient was second gravida. Out of the 92 women who delivered at term, 55 were primigravida, 25 were G2 and 14 were G3.

The gravidity of patients who delivered preterm and who delivered at term have no significant difference as p value is 0.9

**Table 2: Distribution of the participants in terms of gravidity**

Variable	Preterm(11)	Percentage	Term(92)	Percentage	P value
G1	10	90.90	55	59.78	0.99
G2	1	9.09	23	25.00	
≥G3	0	0	14	15.22	
<b>Total</b>	<b>11</b>	<b>100</b>	<b>92</b>	<b>100</b>	





**Figure 2: Distribution of patients with respect to gravidity**

The gestational age of term delivery group was found to be  $32.13 \pm 2.09$  months and for term delivery group it was found to be  $31.79 \pm 1.88$  months at the time of ultrasound examination.. There was no significant difference found in the gestational age at time of ultrasound as the p value was calculated as 0.611.

The gestational age of patients who delivered preterm was found to be  $35.36 \pm 0.92$  months and patients who delivered at term was found to be  $38.56 \pm 0.61$  months. There was significant difference found in the gestational age at time of delivery for both the groups as the p value was calculated as 0.001.

**Table 3: Gestational age at Time of Delivery**

Variable	Preterm(11)	Term(92)	P value
< 37 weeks	11	0	0.001
>37 weeks	0	92	
Mean± SD	35.36364±0.924416	38.56522± 0.616697	

**Table 4: Descriptive statistics**

Variable	Preterm(11)	Term(92)	P value
Gravidity ,median(range)	1(1-2)	1(1-4)	NA
History of Preterm n(%)	1(9.09)	1(1.075)	NA
Output			
cervical length(SD)(mm)	33(5.138093)	37.51087(4.693916)	0.016
Estimated Fetal weight(SD)(kg)	1.8745455(0.4029979)	2.7757143(0.3068128)	0.521
Fetal Zone Depth(SD)	11.972727(3.970917)	8.5978261(2.2640515)	0.0186719
Fetal zone enlargement, %, mean (SD)	0.61827(0.1226673)	0.5358444(0.0587409)	0.0235
Corrected adrenal gland volume, mm <sup>3</sup> /kg, mean (SD)	769.07091(85.343434)	280.5645(38.830805)	0.001

The ultrasound measures of both groups of patients are shown in Table 4. Mean values of the continuous variables like cervical length, estimated fetal weight, fetal zone depth, fetal zone enlargement and corrected adrenal gland volume were tabulated as outcome measures.

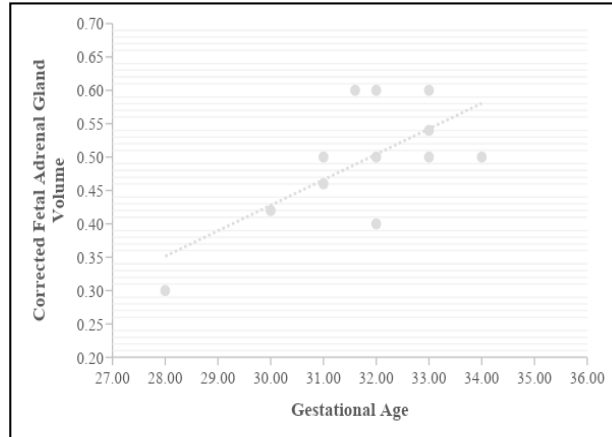
The mean fetal weight in women who delivered preterm was 1.87kg while in those who delivered at term was 2.77 kg with a p value of 0.521.

The test revealed that preterm pregnant women had statistically significant greater fetal adrenal volume and fetal zone depth than those delivered at term. The mean (SD)corrected fetal adrenal gland volume for women who delivered preterm was 769.07 mm<sup>3</sup>/kg and that in the women who delivered at term was 280.564 mm<sup>3</sup>/kg. The p

value was calculated as 0.001 which is statistically significant.

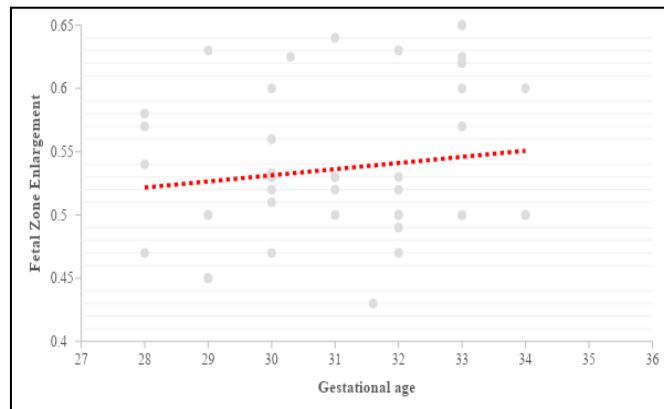
The mean fetal zone depth in patients who delivered preterm was 11.97mm while in those who delivered at term was 8.59. The p value was 0.018 which is statistically significant. Mean fetal zone enlargement in patients who delivered preterm was 0.618 whereas it was 0.535 in patients who delivered at term. The p value calculated was 0.0235 which is statistically significant.

The markers of fetal adrenal gland enlargement i.e. FZE and cAGV showed higher values in the women who delivered preterm than term and that too with statistical significance.



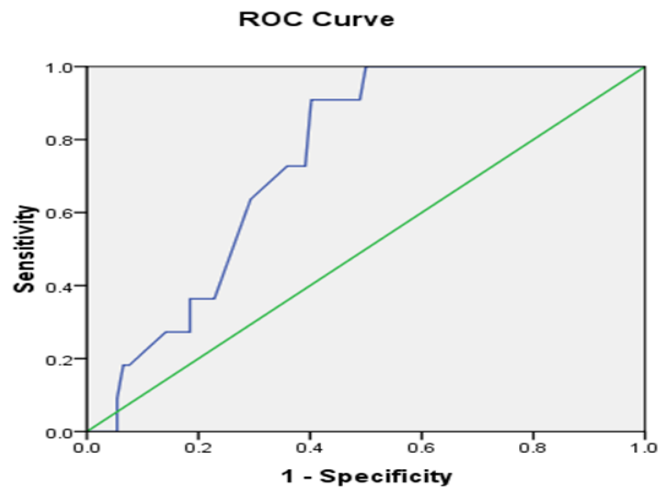
**Figure 3: Linear regression graph between corrected adrenal gland volume and gestational age**

This is a linear regression graph between corrected fetal adrenal gland volume (cAGV) and gestational age. As it can be seen in the scattered plot, there is a positive correlation between gestational age and corrected fetal adrenal gland volume however it is a weak correlation.

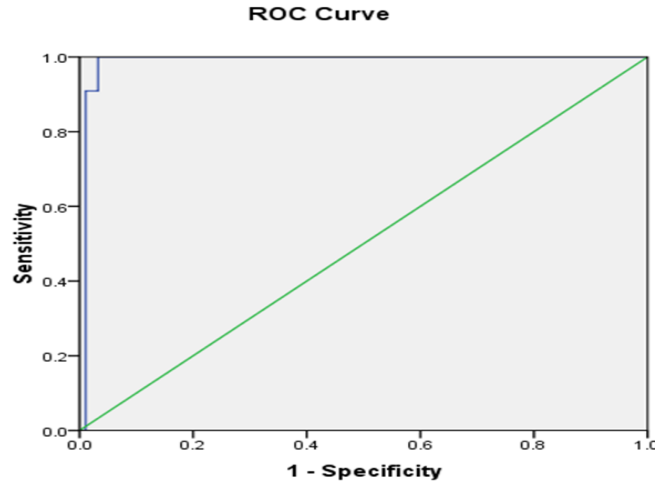


**Figure 4: Linear regression graph between fetal zone enlargement and gestational age**

This is a linear regression graph between fetal zone enlargement and gestational age. As can be seen from the graph, there is no significant correlation between both these variables.



**Figure 5: ROC curve of fetal zone enlargement in the prediction of preterm birth**



**Figure 6 : ROC curve of corrected adrenal gland volume in the prediction of preterm birth**

**Table 5: Sensitivity and specificity of test variables at their ROC curve derived cut off values**

	AUC	Cut off value	Sensitivity	Specificity
<b>Fetal zone enlargement</b>	74.5	58.50	72.7	60.9
<b>CAGV</b>	98.7	632.50	90.9	96.7

ROC curves were plotted with Table 7 showing cut-off values of variables (derived from ROC curves) and their corresponding sensitivities and specificities. cAGV at the cut-off value of 632.50 mm<sup>3</sup>/kg showed the highest area under the curve, AUC (0.987), sensitivity (90.9%), and specificity (96.7%) for prediction of preterm birth. FZE also showed a significant AUC as 0.745, sensitivity as 72.7% and specificity as 60.9 %. Once supported by more comprehensive studies, this result could be beneficial in the prediction of preterm labor in clinical practice.

### Discussion

This study was done in the department of Obstetrics and Gynaecology in SMS Medical College, Jaipur. Pregnant women with 28-34 weeks of gestation with an uncomplicated singleton live pregnancy with or without history of prior preterm births or abortions were included in the study and subjected to ultrasonography wherein fetal adrenal gland biometry including fetal adrenal gland volume and fetal zone enlargement was assessed and cervical length was also measured. These women were followed up till delivery and delivery outcome in the form of preterm or term delivery and their association with these ultrasonographic parameters were assessed.

In our study, out of 103 participants, 11 participants delivered preterm and 92 delivered at term. There was no significant difference between the two groups in terms of distribution of age. Our observation was consistent with the study of Theresia B Temu *et al* (2016)<sup>3</sup> where maternal age was not associated with increased risk of preterm delivery. This is also consistent with the study of Anand Ahankari *et al* (2017)<sup>4</sup> wherein they analyzed 655 live births, of which

6.1% were preterm deliveries. The odds of both preterm delivery and LBW were reduced in multigravida compared with primigravida women regardless of age.

As our hospital caters to majority of the rural population, 91 out of 103 participants had a rural background. This is consistent with the results of Theresia B Temu *et al* (2016) studies which state that preterm birth is less likely in women who reside in urban areas. More importantly, it concluded that women seeking inadequate antenatal care are more likely to have preterm births which are also evident from this study. This is also consistent with the study of Maria do Carmo Leal *et al* (2016)<sup>5</sup> who in their study identified socio-demographic factors associated with spontaneous preterm birth. These were adolescent pregnancy, low total years of schooling, and inadequate prenatal care. Other risk factors were previous preterm birth, multiple pregnancy, abruptio placentae and infections.

The study shows gestational age at the time of ultrasound which shows that patients who delivered preterm had a mean gestation of 32.13 weeks. As mentioned before, being a tertiary care centre catering to a majority of rural population, most of our patients present to the hospital for the first time in their third trimester itself. Thus prediction of preterm birth in patients with no prior antenatal visits becomes very important for timely intervention to reduce the burden of perinatal morbidity and mortality.

The ultrasound examination of patients who delivered preterm and term was done at the same gestational age and there was no significant difference among them. It shows that the examination of fetal adrenal gland biometry and

cervical length was done for both the groups at the same gestational age hence the results were able to predict the risk more appropriately and without any error.

This study shows that patients who delivered preterm had a shorter cervical length than those who delivered at term. The results were coherent with Iams *et al.* (1996)<sup>6</sup> who performed secondary analysis on data collected for the Preterm Prediction Study, and found that the rate of cervical shortening was higher in women who went on to have spontaneous preterm birth. Similar results were observed in other studies as well.

This study shows that corrected fetal adrenal gland volume and fetal zone enlargement is significantly higher in patients who delivered preterm than at term. This is consistent with studies done previously viz Turan *et al.* (2007)<sup>7</sup> prospectively assessed the relationship between fetal adrenal gland volume measurement by 3D ultrasound and preterm birth (birth < 37 weeks) in 150 women. Sixty-seven women delivered at term and were considered “normal” pregnant controls. Fetal adrenal gland volume and kidney volume changed significantly in a direct linear relationship with estimated fetal weight (fetal adrenal gland volume  $r=0.88$ ,  $P<.001$ ; kidney volume  $r=0.81$ ,  $P<.001$ ). It was determined that a corrected adrenal gland volume index of more than 422 mm<sup>3</sup>/kg was able to predict preterm birth within 5 days from the date of the scan with the highest accuracy (receiver operating characteristic area: 0.957, 95% confidence interval 0.91–0.99). The sensitivity, specificity, and positive and negative likelihood ratios were 92.0%, 99.0%, 93.5, and 0.08, respectively.

It also concluded that fetal zone enlargement (d/D or FZE) of more than 49.7% was found to be 100% sensitive.

Similarly, Shubhra Agarwal, Arjit Agarwal *et al.* (2017)<sup>8</sup> wherein thirty pregnant females (from 28 to 37 weeks of gestational age), showing clinical signs and delivery outcome of preterm birth were included in the study with an equal number of not-in-labor antenatal females at 37 weeks as controls. Among 30 pregnant females as case and another 30 as controls, fetal zone enlargement showed the sensitivity and specificity (90% and 80% respectively) in the prediction of preterm birth. Shear wave speed estimation of the antenatal cervix showed the highest sensitivity and specificity (96.7% and 87% respectively) in the prediction of preterm birth and also showed a strong correlation with fetal adrenal gland enlargement. Fetal adrenal zone enlargement was also shown to be a reliable marker of preterm birth, however, with reduced sensitivity and specificity than shear wave speed. They also found that cAGV was higher in preterm deliveries with 67% sensitivity and 76% specificity at cut-off value of 415 mm<sup>3</sup>/kg ( $p < 0.001$ ).

This is also consistent with the study of Chandana S Bhat *et al.* (2018)<sup>9</sup> wherein among 204 women who developed

features of preterm labor eventually had a significantly high cFAGV (404.70 mm<sup>3</sup>/kg body weight) during the first scan compared to those who reached term asymptotically (241.35 mm<sup>3</sup>/kg body weight). A cutoff value of 271.16 mm<sup>3</sup>/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.

This is also consistent with A C Gimovsky *et al.* (2019)<sup>10</sup> which was a diagnostic test accuracy study using a prospective cohort design evaluating the ability of 2-dimensional ultrasound measurement of fetal adrenal gland total length, total width, fetal zone length and fetal zone width in women in the third trimester to predict the primary outcome of spontaneous term labor. Secondary outcomes were vaginal delivery, length of labor, and maternal and neonatal morbidities.

Of 43 patients recruited, 3 were excluded. 11 presented in spontaneous labor and 29 underwent induction of labor. Patient demographics were similar for all included except for admission cervical exam and oxytocin use. A receiver operative curve was created to assess test predictability. Weighted width of fetal adrenal gland was the best predictor of spontaneous labor amongst variables measured with an area under the curve of 0.674,  $p = 0.93$ .  $w/W \geq 0.41$  had a sensitivity of 91.0%, specificity of 44.8%, positive predictive value of 38.5% and a negative predictive value of 92.3%. Maternal and neonatal morbidities were not different between the spontaneous labor group and the induction of labor group. It was concluded that ultrasound measured fetal  $w/W$  was moderately predictive of spontaneous labor.

In the study by H M Abo Shady *et al.* (2020)<sup>11</sup> thirty-three preterm pregnant women at 29-36 weeks of gestation with single pregnancy and clinical diagnosis of preterm labor and control group of 33 pregnant women at 37-40 weeks with term pregnancy were included in this study. Fetal Zone Depth and Total Gland Depth (TGD) of fetal adrenal gland were ultrasonographically measured and FZD/TGD ratios were calculated and compared between the two groups. No difference was found between the two groups in respect of age and number of pregnancies ( $P > 0.05$ ). Yet, preterm birth history rupture of membrane, cervical dilatation and mode of delivery were higher in preterm group ( $P < 0.05$ ). Fetal adrenal gland FZD/TGD ratio was statistically significantly higher in preterm group compared to the term group ( $52\% \pm 5\%$  vs.  $29\% \pm 9\%$ ;  $P < 0.001$ ). The growth in FZ as a fetal adaptation mechanism in increased fetal stress in preterm labor cases was at a significant level. This is consistent with this study wherein the mean fetal zone depth in patients who delivered preterm was 11.97mm while in those who delivered at term was 8.59mm. The  $p$  value was 0.018 which is statistically significant. Mean

fetal zone enlargement in patients who delivered preterm was 0.618 whereas it was 0.535 in patients who delivered at term. The *p* value calculated was 0.0235 which is statistically significant.

This is also coherent with the study by J Goletzke et al (2020)<sup>12</sup> in which fetal adrenal gland was assessed via transabdominal ultrasound at gestational weeks (gw) 24–26, 28–30, and 34–36 in a low-risk pregnancy cohort. Longitudinal trajectories of the total gland and the mark (so called fetal zone) as well as ratio of fetal zone width/ total widths (w/W) were analyzed using repeated ANOVA analyses. To compare trajectories of the ratio w/W for preterm and term fetuses respectively, as well as women with and without clinical signs of preterm labor, the propensity score method was applied. Fetal zone width increased over the course of pregnancy ( $p < 0.0001$ ), while the ratio w/W decreased ( $p < 0.0001$ ) ( $n = 327$ ). Comparing the trajectories of the ratio w/W in fetuses born preterm ( $n = 11$ ) with propensity-score matched term born fetuses ( $n = 22$ ), a decrease between gw 24–26 and 28–30 was observed in both groups, which continued to decrease for the term born fetuses. However, in preterm born fetuses, the ratio increased above the term born values at gestational age 34–36. This study provided longitudinal growth data on the fetal adrenal gland and supports the hypothesis that fetal zone enlargement is associated with preterm birth which could play an important role in risk-prediction.

### Conclusion

The present study demonstrates that preterm delivery is still a challenge in our country. Majority of the risk factors, found to be associated with preterm birth, are modifiable. Modifiable risk factors can be identified and modified as primary prevention strategies. Risk factors like previous preterm birth, multiple pregnancies and placental abnormalities cannot be modified hence preventive efforts should be directed towards modifying working conditions during current pregnancy. Therefore early identification of these factors during prenatal care may prevent the risk of preterm delivery. This calls upon to reinforce antenatal care and services for better birth outcomes. Appropriate and innovative preventive intervention, customized individual needs may prevent preterm births and improve fetal outcomes. Therefore, secondary prevention in terms of screening with novel, more sensitive and specific markers like fetal adrenal gland volume and fetal zone enlargement even in the third trimester can aid in reducing the burden of mortality and improve the perinatal outcome in comparison to the established cervical length assessment. Ultrasound being noninvasive, easily reproducible and a cost effective screening method has the potential and feasibility of being of utmost importance to combat preterm birth. Fetal adrenal gland biometry can act as a potential new marker for the

prediction of preterm delivery. In order to reach an effective reduction in preterm births, two premises are necessary: to identify women who are at risk by screening with assessment of fetal adrenal biometry and cervical length and to dispose of measures that serve to extend pregnancy by timely interventions and instituting measures.

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