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Original Research Article

Role of Antenatal Ultrasound in Prediction of Preterm Birth by Using Fetal Adrenal Gland Biometry

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Abstract

Background: Preterm birth is a major cause of perinatal morbidity and mortality worldwide. Timely identification of women at risk of preterm birth is crucial for appropriate management. Fetal adrenal glands play significant role in initiation of labor and can be assessed using ultrasonography for predicting onset of labor.

Method: Prospective study done on 260 pregnant women of >28 weeks of gestation. 10 women were lost to follow up, so final analysis included 250 women. Ultrasonographic measurements of width (FAZW), length (FAZL), and depth (FAZD) of "fetal zone" of the fetal adrenal gland and the width (FAGW), length (FAGL) and depth (FAGD) of the total gland were taken. Ratios of each measurement (FAZW/FAGW, FAZL/FAGL and FAZD/FAGD) and corrected fetal adrenal gland volume (cFAGV) were calculated. Patients were followed up till delivery, whether term or preterm and outcomes correlated with fetal adrenal gland parameters.

Result: The cFAGV, depth ratio and width ratio were significantly higher in women who delivered preterm. FAZD/FAGD had the best efficacy (sensitivity 100%, specificity 80.2%) and AUC of 0.95 with cutoff of 0.5 followed by FAZW/FAGW (sensitivity 94.1%, specificity 84.9%) with cutoff of 0.53. cFAGV with cutoff of 370mm^3/kg body weight also had the same sensitivity as the width ratio but less specificity (79.2%). No significant difference was seen in FAZL/FAGL(P> 0.05).

Conclusion: The ultrasonographic measurements of fetal adrenal gland parameters show high accuracy in prediction of preterm birth and can be used for screening women at risk of preterm delivery.

Keywords: Labor, Fetus, Adrenal Gland, Preterm, Ultrasonography.

Introduction

A preterm birth is one that occurs before the start of the 37th week of pregnancy. Preterm births (PTB) are a major and pertinent cause of perinatal morbidity and mortality. Following PTB, infants can experience significant long-term cognitive, behavioral, emotional, sensory, and motor deficits. [1] Therefore, it is extremely important to identify the women at risk of preterm birth, so that timely preventive and therapeutic measures can be implemented.

Traditional predictors such as obstetric risk factors and clinical cervical assessment or an ultasonographic cervical length measurement are helpful but as time has

evolved, it is found that they are not fairly accurate marker for onset of labor.

The beginning of a parturition is largely dependent on the 'Placental clock' which plays a pivotal role in interrupting the uterine quiescence and thus initiating onset of labor. [2] It works through placental corticotrophin-releasing hormone (CRH), which in turn causes activation of the fetal hypothalamic pituitary-adrenal axis. Interactions between placental and fetal adrenal gland endocrine signaling pathways takes place [3] and it leads to increased production of dehydroepiandrosterone-sulfate (DHEA-S) by the 'fetal zone' of the adrenal gland. As a result, the entire fetal adrenal gland grows in size. [4]

This knowledge imparts a clue that fetal adrenal gland measurement in pregnancy can be used as a noninvasive marker for onset of labor. 2-dimensional (2D) ultrasonographic measurements of the fetal adrenal gland can be taken for prenatal identification of this process and prediction of onset of labor.

Material and Methods

Study design:

A hospital based and prospective study, was conducted in the Department of Radio-diagnosis, of a tertiary care hospital in Indore, Madhya Pradesh, India after receiving approval from Institutional Scientific and Ethical Committee. The duration of the study was from March 2021 to August 2022. A total of 260 pregnant females who came for routine obstetric scan and fulfilled the inclusion criteria were selected for the study.

Inclusion criteria was women with singleton pregnancy of > 28 weeks of gestation, while exclusion criteria were pregnancy with suspected fetal growth restriction (sonographic estimated fetal weight < 10th percentile), maternal Systemic illness like hypertension, diabetes mellitus, thyroid and adrenal diseases and gestational complications like pregnancy induced hypertension, preeclampsia, gestational diabetes, fetal congenital anomaly and twin pregnancies.

Study protocol

According to the inclusion criteria, women with uncomplicated singleton pregnancy were selected for the study and after taking the informed consent, PCPNDT registration was done. Gestational age was determined according to the last menstrual period, when it agreed with first trimester ultrasonographic examination. Otherwise, only the later was considered for the same. Ultrasonographic examination of all women were done in supine position, using a low frequency curvilinear transducer (1-8MHz). Both transverse and sagittal planes of fetal adrenal glands are obtained. The fetal adrenal gland nearest to the probe side was taken for the measurements. The length (FAGL) and width (FAGW) of the gland is measured in the transverse plane, whereas the depth (FAGD) of the adrenal gland is measured in the sagittal plane. The fetal adrenal zone is visualized as hyperechoic line in center of the fetal adrenal gland. The length (FAZL) and width (FAZW) of the fetal adrenal zone is noted in the transverse plane and the depth (FAZD) was measured in the sagittal plane. Zone to total gland ratios of the parameters like length ratio (FAZL/FAGL), width (FAZW/FAGW) and depth ratio (FAZD/FAGD) were calculated. The fetal adrenal gland volume (FAGV) was calculated using the ellipsoid formula, (0.523 x length x width x depth). Corrected fetal adrenal gland volume (cFAGV) is obtained from dividing fetal adrenal gland volume by the estimated fetal weight, so as to make it a gestational-age independent factor. Women were followed up and information regarding the timing of delivery was noted and comparison between their fetal adrenal gland measurements was done for analysis.

Statistical analysis:

Data were tabulated in the Microsoft Excel Sheet and SPSS software was used to analyze the data. Mean and standard deviation of quantitative variables were computed. Chi square test to compare demographic data and unpaired t test for comparing adrenal gland parameters in different groups was used and p value of <0.05 was considered statistically significant. (ROC) curve was plotted to obtain the cut-off value and the area under the curve was calculated.

Results

Table 1: Distribution of patients according to demographic data

Number of cases	250	35	215
Age (in years), mean+ SD	24.53±4.2	23.4 ± 3.56	24.7 ± 4.26
History of preterm labor	13	10	3
Primipara	94	24	70
Multipara	156	12	144
MGA at the time of examination (in weeks)	33.7	32.3	33.6
MGA at the time of delivery (in weeks)	37.8	34.6	37.6

- The mean age of total population was 24.53 ± 4.2 years with majority lying in the age group of 21-25 (49.2%) years of age, preterm (64.7%) deliveries were more commonly seen in primipara.
- The mean gestational age(MGA) at the time of examination 33.7 weeks in the total study population with 32.35 weeks in preterm group, 33.60 weeks the in term group.
- The mean age at the time of delivery was 34.6 ± 1.06 weeks in preterm group, 37.6 ± 0.54 weeks in term group as shown in TABLE 1.

Table 2: **Fetal adrenal gland measurements in different groups**

PARAMETER	PRETERM (MEAN)	TERM (MEAN)
FAZW (mm)	4.77	2.90
FAGW (mm)	7.92	6.18
FAZD (mm)	6.61	4.53
FAGD (mm)	11.55	9.89
FAZL(mm)	12.7	11.48
FAGL(mm)	23.33	21.18
FAGV (mm^3)	1087	708.35
cFAGV (mm^3 /kg body weight)	512.15	290.2

- All the fetal adrenal gland parameters like width (FAGW and FAZW), length (FAGL and FAZL), depth (FAGD and FAZD) and volume (FAGV and cFAGV) were higher in the preterm group in comparison to the term group as shown in TABLE 2, FIGURE 1 and FIGURE 2.

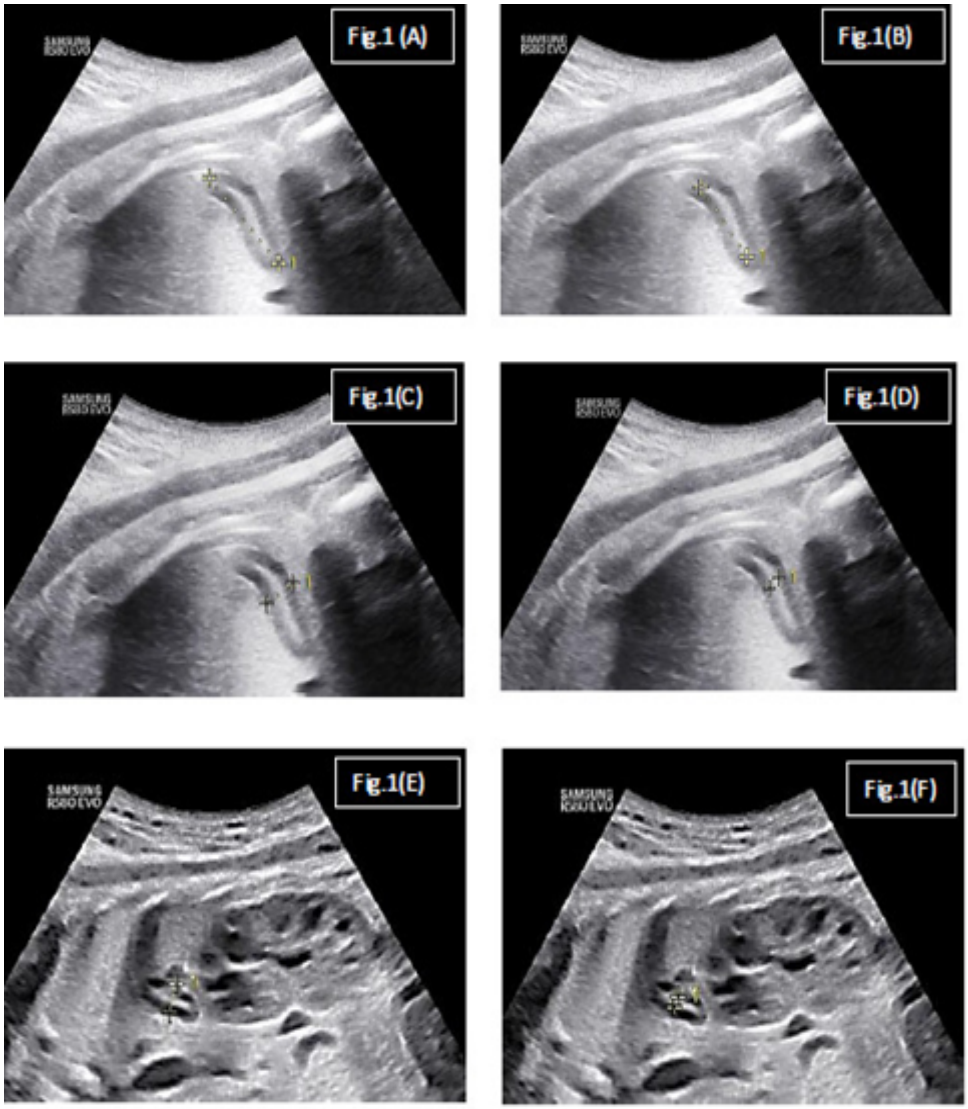

Figure 1: Ultranographic measurements of fetal adrenal glands in a patient who delivered at term

Fig 1 (A-B): Total fetal adrenal gland length measures 21 mm and the fetal zone length measures 11.8 mm in transverse view. The zone length ratio comes out to be 0.56. (C-D): Total fetal adrenal gland width measures 6.3 mm and the fetal zone width measures 2.6 mm in transverse view. The zone width ratio comes out to be 0.41. (E-F): The total fetal adrenal depth measures 5.3 mm and zone depth measures 2 mm. The zone depth ratio comes out to be 0.37 and the cFAGV was 221 mm3/kg body weight.

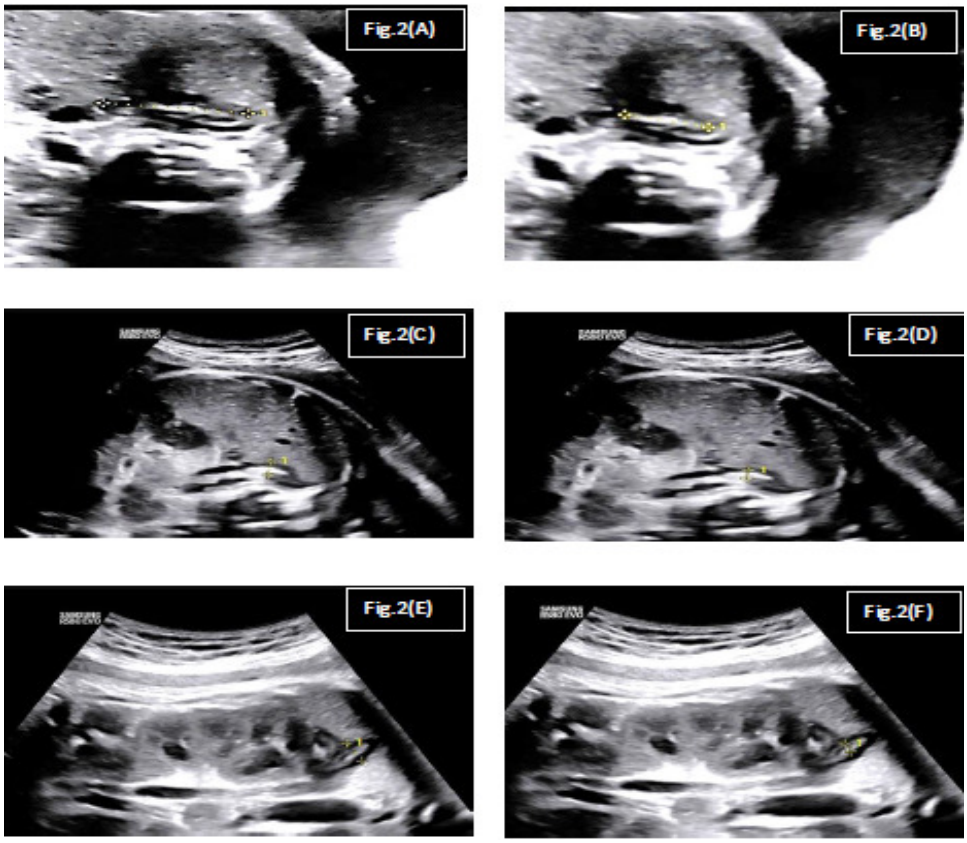

Figure 2: Ultranographic measurements of fetal adrenal glands in a patient who delivered preterm

Fig 2 (A-B): Total fetal adrenal gland length measures 21.6 mm and the fetal zone length measures 12 mm in transverse view. The zone length ratio comes out to be 0.55. (C-D): Total fetal adrenal gland width measures 6.3 mm and the fetal zone width measures 3.7 mm in transverse view. The zone width ratio comes out to be 0.58 (E-F): The total fetal adrenal depth measures 5mm and zone depth measures 2.8 mm. The zone depth ratio comes out to be 0.56 and the cFAGV was 373 mm3/kg body weight.

Table 3: Comparison of Fetal Zone Ratios and Corrected Fetal Adrenal Gland Volume (Cfagv) Between Preterm and Term Group

PARAMETER	PRETERM (MEAN ± SD)	TERM (MEAN ± SD)	P Value
FAZD/FAGD	0.56 ± 0.03	0.45±0.05	<0.01 (significant)
FAZW/FAGW	0.59 ± 0.04	0.48 ± 0.06	<0.01 (significant)
FAZL/FAGL	0.54 ± 0.03	0.53±0.04	0.65(non-significant)
cFAGV (in mm3/kg body weight)	512.15 ± 111.5	294.2 ± 98.8	0.001(significant)

- The fetal zone width ratio, depth ratio and corrected fetal adrenal gland volume were significantly higher in the preterm group as compared to the term group; P value <0.05. However, no significant difference is noted in the length ratio as shown in TABLE 3, FIGURE 1 and FIGURE 2.

Table 4: Comparison of the efficacy of various parameters (with roc determined cutoff values) in prediction of preterm delivery

FAZD/FAGD	0.505	100%	80.20%	45.33%	100%
FAZW/FAGW	0.535	94.10%	84.90%	50%	98.91%
FAZL/FAGL	0.555	44.10%	71.70%	19.74%	88.89%
cFAGV	370.29	94.10%	79.20%	42.11%	98.83%

- On comparing fetal adrenal gland parameters (with ROC determined cutoff values), we found a statistically significant difference between women who had a preterm delivery and those who progressed till term. Fetal adrenal gland depth ratio had the best efficacy (sensitivity 100%, specificity 80.2%) followed by width ratio (sensitivity 94.1%, specificity 84.9%). cFAGV also had the same sensitivity as the width ratio but relatively less specificity (79.2%).

Table 5: Comparative analysis of various parameters using the receiver operating characteristics(roc) curve

FAZD/FAGD	0.95	0.013	< 0.01
FAZW/FAGW	0.94	0.016	< 0.01
FAZL/FAGL	0.54	0.056	0.377 (non-significant)
cFAGV	0.92	0.019	< 0.01

- The area under curve for FAZD/FAGD, FAZW/FAGW and cFAGV was >0.9 which shows that they are excellent predictors of preterm birth. Out of these FAZD/FAGD has the maximum value (0.95) with highest predictive efficacy for pre-term birth, followed by FAZW/FAGW (0.94) and cFAGV (0.92).

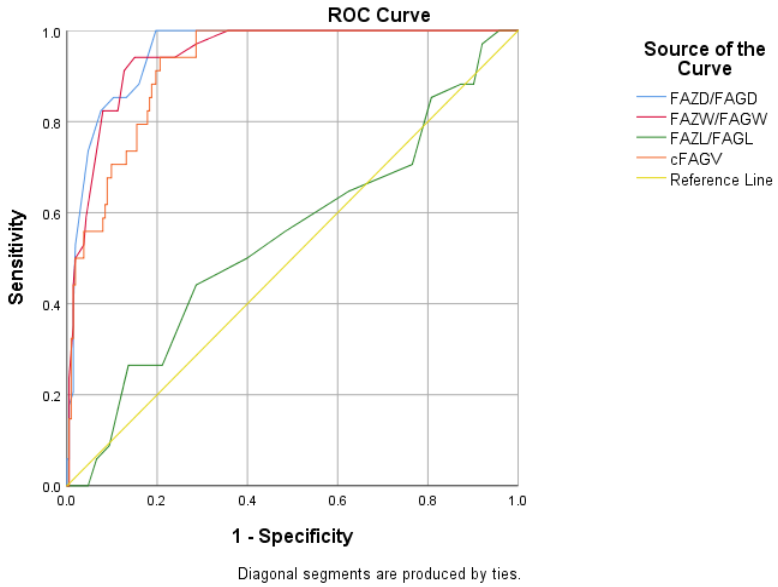

Figure 3: Comparative analysis of various parameters using the receiver operating characteristics (roc) curve for prediction of preterm delivery

- Out of all the parameters FAZD/FAGD has the maximum AUC value (0.95) with highest predictive efficacy for preterm birth, followed by FAZW/FAGW (0.94) and cFAGV (0.92)

Discussion

A total of 260 pregnant women on the basis of inclusion criteria were selected for this study, which was conducted in the Department of Radiodiagnosis of our hospital. The fetal adrenal glands of pregnant females were assessed radiologically using ultrasonography, the women were followed up till the delivery of baby. Out of the total 260 women who were enrolled for the study, 10 women were lost to follow-up. Thus, a total of 250 women were included in the final analysis study.

Out of total 250 pregnant women, 215 (86.2%) women reached term without any complication, whereas 35 (13.9 %) women delivered pre term.

The mean age of the studied women who delivered pre term was 23.4 ± 3.56 years (range 19-34 years), while who delivered at term was 24.7 ± 4.26 years (range 18-41 years). The mean age of total women in our study was, 24.53 ± 4.2 years with majority lying in the age group of 21-25 years of age. The mean age of population in our study was less than those conducted by Bhat et al (2019) [5] (mean age 27.2 ± 3.72 years), Turan et al (2011) [6] (mean age 26 ± 6.38 years).

Preterm deliveries were more common in primiparas 24 out of 35 (64.7%) than multipara 12 out of 156 (35.4%), which was similar to study done by Santipap et al (2018) [7] 58.6% women in preterm group were primipara. Out of 35 women who delivered preterm, 10 (28.5%) women had history of previous pre term delivery, which is similar to the study done by Turan et al (2011) [6] (8 women out of 34 (25.8%) and Bhat et al (2019) [5] (8 women out of 30 (26.6%). It is well known that a history of prior pre term birth is a risk factor for a preterm delivery.

In our study we found that the depth ratio(FAZD/FAGD) was more in the women who delivered preterm (0.56) than in the term group (0.45), which supports the hypothesized etiology of pre term labor i.e. increased steroidogenic activity from the fetal zone leading to fetal zone enlargement and induction of labor. This is comparable to the studies done by Bhat et al (2019) [5] (FAZD/FAGD, 0.55 and 0.46 in preterm and term group respectively, p value=0.02), Turan et al (2011) [6] (Fetal zone enlargement(FZE) 59.9% and 40.6% in preterm and term group respectively; p value <0.01, Shady et al (2021) [8] FZD/TGD ratio was statistically significantly higher in preterm group compared to the term group (52% ± 5% vs. 29% ±9%; P <0.001), Guler at el (2015) [9] FZD/TGD ratio was higher in preterm birth group, compared to the term birth group (p value <0.01).

By plotting the ROC curve, the cutoff value of 0.5 was obtained with a sensitivity and specificity of 100% and 80% respectively which was similar to Turan et al (2011) [6], (cut off value 0.49, sensitivity 100% and specificity 89%), Bhat et al (2019) [5] (cutoff 0.59, sensitivity 100% and specificity 89%), Ibrahim et al (2015) [10] (cut off 0.47, sensitivity 92.6% and specificity 89.6%).

Similarly, the ratio of the fetal zone width and the total gland width (FAZW/FAGW) came out to be more in preterm group (0.59 ± 0.04) than the term group (0.48 ± 0.06), which was statistically significant (p value <0.05), and was similar to the previous studies done by Bhat et al (2019) [5] (FAZW/FAGW ,0.62 and 0.42 in preterm and term group respectively, p value =0.00), Gimovsky et al (2019) [11] (FAZW/FAGW ,0.67 and 0.40 in preterm and term group respectively; p value <0.01). [12]

By plotting the ROC curve the cutoff value was found to be 0.53 with a sensitivity and specificity of 94% and 85% respectively. Bhat et al (2019) [5] found a cutoff of 0.71, with similar sensitivity 96.67% and specificity 86.2%. However, in a study done by Turan et al (2011) [6] the sensitivity of this parameter was found to

be less than the depth ratio and cFAGV (cutoff 0.51, sensitivity 74.3%, specificity 85.2%).

On comparison of fetal adrenal gland length (FAZL/FAGL) in women delivering at preterm and at term, no significant difference was found (0.54 ± 0.03 and 0.53 ± 0.43 in pre term and term group). Bhat et al (2019) [5] also observed similarly, with no significant difference in length ratio was noted between preterm and term group. The cut off value obtained by ROC curve (0.55) showed sensitivity of 44% and specificity of 71%, this shows that fetal adrenal gland ratio is not a useful marker for screening of women at risk of pre term birth.

We also found that women, who had preterm labor eventually, had a significantly high cFAGV (512 mm^3/kg body weight) during scan compared to those who delivered at term asymptomatically (294.4 mm^3/kg body weight; p value <0.01. This was in concordance with previous studies done by Bhat et al (2019)[5] (422.34 mm^3/kg body weight in preterm group and 241.2 mm^3/kg body weight in term group), Turan et al (2011)[6] (561.3 mm^3/kg body weight in preterm group and 329.2 mm^3/kg body weight in term group.

On plotting a ROC to determine the cut-off value of cFAGV, area under the curve was 0.92, with the cut-off value of 370.29 mm^3/kg body weight and showed 94% sensitivity and 79.2% specificity in predicting women who are at risk of delivering pre term. Bhat et al (2019)[5] determined the cut-off value of 348.78 mm^3/kg body weight (96 % sensitivity and 83% specificity, Turan et al (2011)[6] 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.

All these findings suggest that as during preterm labor, due to increased steroidogenic activity in the fetal adrenal zone, the size and volume of the whole fetal adrenal gland increases and with a disproportionate increase in size of the "fetal zone" in comparison to the remainder of the gland and that fetal adrenal gland depth ratio (FAZD/FAGD) had the best efficacy (sensitivity 100%, specificity 80.2%) in prediction of preterm delivery, followed by width ratio (sensitivity 94.1%, specificity 84.9%) and cFAGV (sensitivity 94.2%, specificity 79.2%).

Conclusion

The results obtained in our study propound that there is relationship between onset of labor and increased fetal adrenal zone parameters which shows that important role is played by the fetal adrenal glands in the endocrine regulation of parturition and 2D ultrasonographic assessment of fetal adrenal gland volume and fetal zone enlargement can be a non-invasive and cost effective potential screening method which is beneficial and can be routinely done for the prediction of preterm birth especially in the third trimester.

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