

To Evaluate Transabdominal Ultrasound Measurement of Fetal Adrenal Gland at Period of Gestation 22 Weeks to 28 Weeks and Study its Correlation with the Period of Onset of Labour (Term/Preterm)

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ABSTRACT

Introduction: Prediction of preterm labour is a challenge for obstetrician. Preterm births are one of the major contributors towards perinatal mortality and morbidity. Study Aimed to evaluate and correlate ultrasound measurements of fetal adrenal glands at 22 to 28 weeks of period of gestation (POG) with time of onset of labour (Term/Preterm).

Material and methods: Fetal adrenal gland biometry of 180 antenatal women was done along with detailed obstetric ultrasound at a POG of 22 to 28 weeks in the Department of Obstetrics and Gynecology in association with Department of Radiodiagnosis to correlate the fetal adrenal gland volume with the onset of labour term or preterm after obtaining IEC clearance.

Results: On observing these 180 women during the onset of labour, 22 women had preterm labour, the optimal cut off being 548mm³/kg with high sensitivity, specificity, positive and negative predictive value.

Conclusion: The corrected fetal adrenal gland volume (cFAGV) can be used as a predictor for onset of labour - term or preterm.

Keywords: Fetal Adrenal Gland Volume, Preterm Labour, Ultrasonography

INTRODUCTION

The process of childbirth in humans is a complex phenomenon involving change in hormones relating to the chemical and mechanical processes coming into play.¹ Disagreement amongst researchers on the factors which could lead to onset of labour is a growing concern amongst the care providers.² Different organs with their release of hormones have been studied as a predictor for onset of labour, whether term or preterm. Fetal adrenal gland is receiving an increasing attention for the same. The fetal adrenal gland has endocrine function and becomes active in utero. The gland is involved in regulating the response of fetus to hypoxia which has been implicated in onset of labour.³

Preterm birth has been a concerning health problem in most countries whether developed or developing despite medical progresses.⁴ There is a cascade of events that trigger the onset of labour in humans. The 'Placental Clock' plays an important role in interrupting the dormancy that the uterus is in and so starting a sequence of events triggering onset of labour. The activation or enlargement of the adrenal gland is caused by the placental corticotropin releasing hormone which is a mediator of this placental clock.⁵

The adrenal gland has a very high vascularity and is required for the development of adrenal cortex and the production of steroidal hormones.⁶ The volume of the fetal adrenal gland enlarges in the last 6 weeks before delivery especially with the disproportionate increase between the central and the peripheral areas. Hence, the high vascularization would be necessary to increase the volume of this gland which can be detected by the reduced resistance of the fetal adrenal artery.⁷ Therefore, to know the women who are at a risk for preterm birth, is a necessity for early intervention and for better obstetric outcome. For the last many years, considerable number of attempts have been made towards determining a precise method to predict labour before term. Previous methods such as clinical presentation, cervical length and history of the patient were not very helpful in determining the population at risk of preterm.

MATERIAL AND METHODS

The present prospective observational study was done in MMMCH, Kumarhatti Solan Himachal Pradesh in 180 antenatal women (March 2020 – August 2021). After the approval of the institutional ethics committee.

The study included pregnant women of age 21-35 years having singleton pregnancy with POG 22 to 28 weeks irrespective of the parity who had conceived spontaneously. Women with overt hypertension, eclampsia, overt/gestational diabetes mellitus, severe UTI, multiple pregnancies, placenta previa, hemoglobin less than 9 g/dl, history of threatened abortion, USG diagnosed anomalies incompatible with life, oligohydramnios, polyhydramnios, maternal heart

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disease, history of cervical surgery/ prolapse and artificial reproductive technique conception were excluded.

Ultrasonographic imaging

All women who consented to participate were subjected to 2-dimensional ultrasonic measurement of fetal adrenal gland after filling up of PCPNDT forms duly signed by the patient and the radiologist.

Ultrasonography imaging machine used for all cases was Phillips Affiniti 70G Ultrasound bearing Sr. No. USN17F1419 registered under PCPNDT Act. Detailed obstetric scan along with multiple fetal growth parameters was also recorded.

Fetal adrenal gland biometry

Fetal adrenal gland assessment was done on the same ultrasound system using curvilinear transducer of 3–6 MHz frequency. Fetal adrenals were focused in the axial plane, by smoothly navigating the transducer cranially above the level of kidneys. The length and width of both fetal adrenal glands were calculated and fetal adrenal volume was assessed by using ellipsoid formula (length *width*depth*0.532). These measurements were done on both adrenal glands.

EFW was calculated automatically using Hadlock45 formula based on four common fetal measurements i.e., biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL).

STATISTICAL ANALYSIS

The clinical and sonographic data was stored on separate spreadsheets for preterm and term groups (after delivery) using Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, USA). All statistical analysis was done using SPSS Statistics software for Windows (Version 25.0. IBM Corp., Armonk, NY, USA). Receiver operating characteristics (ROC) curve was used to determine for all the variables to obtain their best predictive cut-off values. The level of statistical significance was determined. The degree of agreement and proportional bias between the measurements of both adrenal glands was investigated.

RESULTS

The mean age of subjects was 26.7±3.61, majority from the urban area. The primigravida enrolled for the study were 104 out of 180. The mean gestational age at enrollment to the study was 25.3±1.89 weeks. The adrenal gland volume was measured for both left and right fetal adrenal glands.

The corrected adrenal gland volume of both adrenal glands was taken between 22 – 28 weeks gestation which was calculated by dividing adrenal gland volume in mm³ by the estimated fetal weight in Kg for that particular case and the maximum number of cases were within the volume range of 30 to 230 mm³ per Kg.

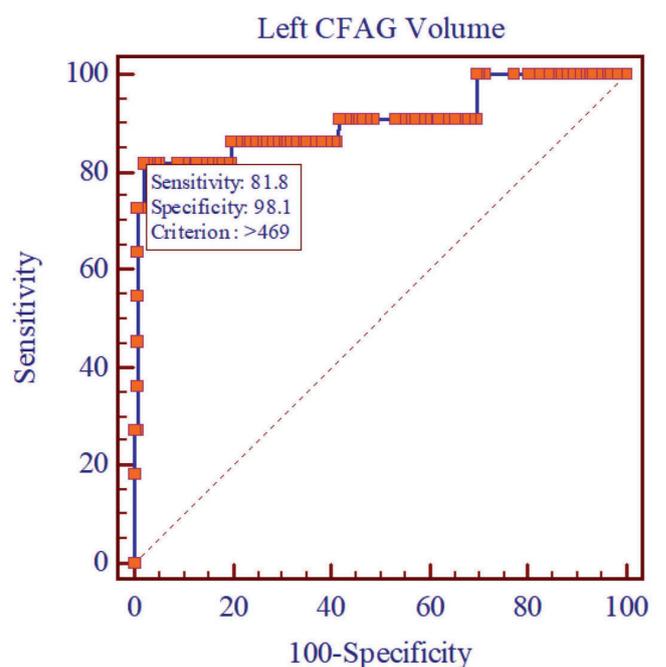
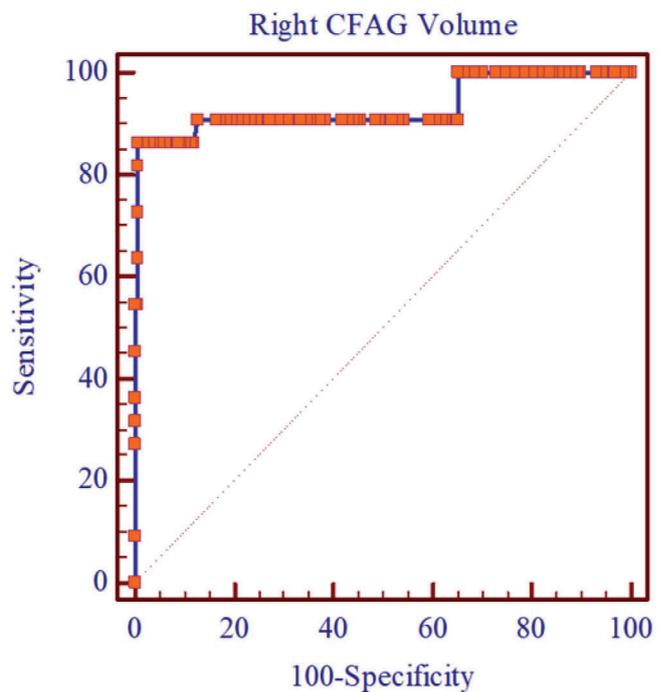
The corrected adrenal gland volume was plotted on the ROC curve to get the optimal cut-off, sensitivity, specificity, positive predictive value, negative predictive value for the prediction of preterm labor in the studied subject. The ROC curves were plotted for both the right and the left fetal adrenal glands separately.

Sr. no.	Observation	Mean
1	Age	26.7 ±3.61 years
2	Gestation at enrollment	25.3±1.89 weeks

Table-1: Demographic data

Sr. no.	Observation	No of subjects
1	Parity	
	Primigravida	104
	Multigravida	76
2	History of abortion	26
3	History of previous preterm	12

Table-2: Obstetric history of the subjects



Fetal adrenal gland	Cut off Mm ³ /kg	Sensitivity(%)	Specificity(%)
Right	628	81.8	99.4
Left	469	81.8	98.1

Table 3: Cut-off , sensitivity and specificity of both adrenal glands

Fetal adrenal gland	Positive predictive value	Negative predictive value
Right	94.7	85.7
Left	97.5	97.6

Table 4: Positive and negative predictive value of the fetal adrenal glands

Out of the 180 patients, 22 delivered preterm and 158 progressed to term. The optimal cut off obtained after plotting the right cFAGV on the ROC curve of was 628 mm³/Kg. Sensitivity was 81.8%, specificity -99.4%, positive predictive value- 94.7%, negative predictive value – 97.5% Similar results were obtained for the left gland as well. The elective LSCS were 5 out of 180 for the indications like cephalopelvic disproportion, previous LSCS and fibroid with pregnancy. Out of 175 subjects, 61.1% (110 cases) had spontaneous onset of labour rest 36.1% had induced labour at term for maternal and fetal indications. The adrenal gland volume was found higher in subjects who had spontaneous onset of labour in term as compared to those who underwent induction but it was not statistically significant.

DISCUSSION

The diagnosis of onset of labor has a significant importance in maternity care; there are multifaceted factors that trigger this phenomenon; however, due to large disagreement in opinions, there has been a growing concern among health care providers to study the possible factors that precisely correlate with the onset of labor. The present study aimed to evaluate the role of fetal adrenal gland volume at 22 to 28 weeks period of gestation in the prediction of onset of labor. We included 180 antenatal women between POG 22 weeks to 28 weeks who qualified the inclusion criteria and gave a written consent. The average age of patients was observed as (26.7±3.61) years and the most common age group was (20-35) years, constituting about 54% patients. Three social parameters were considered for patients: area, socio-economic status and educational background. In the present study we found that majority of the patients were from urban area constituting (86.7%) and only (13.3%) were from rural area. The reason for lower percentage of patients from rural areas may be attributed to the fact that our institution is situated in rural area and the rural areas of Himachal are thinly populated. The maximum number of patients were from lower middle class category accounting for (52.8%) followed by the upper middle class category (21.7%). We observed that only 3 pregnant women were illiterate and majority of the studied subjects were literate (98.3%), of them (20.6%) were educated up to high school level, (17.2) were undergraduates, (34.4%) were graduates and (26.1%) were post-graduates. Obstetric history was categorized

primigravida and multigravida, we observed that (58%) were primigravida and (42%) were multigravida; however, the difference was statistically insignificant. These results are in conformity with study conducted by Bhat et al who also reported a maximum percentage of primigravida patients in a likewise study². There were total of 26 abortions, of them (08) had 2nd gravidity and first abortion, (12) had 3rd gravidity and first abortion, (02) had 4th gravidity and first abortion and (04) had 4th gravidity and 2nd abortion. In the present study, the mean gestational age was found to be (25.3±1.89) weeks with majority of patients (31.7%) falling in (26-27) weeks of gestation followed by (30%) falling in (24-25) weeks of gestations. In a study conducted by Bhat et al the average gestational age of patients at admission was reported as (32.27 ± 1.25) weeks². We measured volume of fetal adrenal gland by using the ellipsoid formula (0.523 * length * width *depth), all the patients were attended by a same sonographer so as to avoid any possible human bias. Parturition and labor onset is not a simple and straight biological process; in fact, it is a hormone-based loop which resides with the activation of fetal hypothalamus and pituitary glands stimulated by fetal stress. This eventually activates the fetal adrenal gland where the central zone of the gland responds by releasing glucocorticoids, predominantly DHEA-S. Subsequently the interaction of fetal adrenal gland and placenta upregulates placental CRH, which in turn causatively releases prostaglandins like PGE2 and PGF2a, this phenomenon ultimately leads to onset of labor^{8,9}. Hence early commencement of placental CRH turns into a biological clock in early onset of labor and delivery^{10,11}. We observed that average volume of left and right adrenal gland was (411.3±288.01) and (355.8±15.29) mm³ respectively. Estimated fetal weight at that gestation is required to calculate the corrected fetal adrenal gland volume to make it independent of gestational age, which in turn is calculated from different parameters at that gestational age obtained by USG. We determined multiple fetal growth parameters like, BPD, HC, AC and FL (cm) to estimate fetal weight using Hadlocks formula . We calculated corrected left and right fetal adrenal gland volume and found that the difference is significant with a p-value of 0.398, the optimal cut-off for right and left adrenal gland was respectively observed as 628mm³/kg and 469mm³/kg, the subjects that had CFAG volume of more than 628 were 19 out of which 18 had preterm delivery

and 1 had term delivery and 4 subjects with CFAG volume less than the optimal cut of 628mm³/kg delivered preterm. The subjects that delivered as preterm with right adrenal gland cut off value > 628mm³/kg interestingly had left adrenal gland cut off value >469mm³/kg. Numerous studies have been conducted on volume of fetal adrenal gland; for instance, Turan et al¹² also reported higher volume of fetal adrenal gland born as preterm, authors observed corrected adrenal gland volume of more than 422mm³/kg. We performed sensitivity analysis of the diagnostic accuracy of both right and left corrected fetal adrenal gland volume in predicting the onset of preterm <37 weeks labor and observed that for right adrenal gland; the sensitivity was (81.8%) specificity was (99.4%), positive predictive value was (94.7%), negative predictive value was (97.5%) and the area under ROC curve was 0.933 with the confidence interval between (0.886-0.965). And for the left adrenal gland; the sensitivity was (81.8%), specificity was (98.2%), positive predictive value was (85.7%), negative predictive value was (97.6%) and the area under curve was (0.904) with the confidence interval between (0.852-0.943). The correlation of both right and left corrected adrenal gland volume with the onset of labor was insignificant which means that sensitivity and specificity of both glands and the preterm deliveries are statistically same in both the glands. In consonance to the literature, Turan et al reported the cut-off value of corrected fetal adrenal gland volume greater than 422 mm³/kg with a sensitivity of 92% and specificity (99%). Same authors later¹⁰ proposed the cut-off value of 420mm³/kg with 81% sensitivity and 87% specificity; however, Hoffman et al found contrary results by reporting spontaneous preterm births with smaller adrenal gland volume¹³. Contemporary to our observations several authors have reported likewise results; Agarwal et al reported higher volume of corrected adrenal gland in case of preterm deliveries with 67% sensitivity and 76% specificity at the cut-off value of 415 mm³/kg¹⁴. Bhat et al also reported that women having a corrected fetal adrenal gland volume of 271.16mm³/kg were prone for developing risk features for preterm labour on the basis of scan performed between 28 and 34 weeks with sensitivity 90% and specificity 8.9%². Some authors employed multiple logistic regression analysis to signify that corrected adrenal fetal gland volume is independent predictor for preterm births within 5 days of measurement^{15,16}. Guler et al conducted a study to compare the fetal zone depth (FZD) of fetal adrenal gland in term and preterm labour cases and observed that in preterm labor cases the growth of fetal zone as a fetal adaptation mechanism is significantly increased compared to term labour case¹⁷. The assessment of fetal adrenal gland was performed by a good corpus of scholars and most of the findings independently revealed that risk of preterm birth increases with increase in volume of corrected fetal adrenal gland. Different techniques were employed for precisely locating the adrenal gland for optimal measurements; Lijima et al used right adrenal gland measurements instead of left adrenal gland¹⁸ because some researchers had previously reported less variability in right adrenal gland. However, these studies paid attention on

either corrected fetal adrenal gland volume or fetal adrenal gland width ratio but our study explicitly focused on the prediction of preterm labor with both left and right corrected fetal adrenal gland volume. We comprehensively analyzed the spontaneous and induced preterm labor cases whereby we came to know that 175 patients had onset labor, out of which 110 were spontaneous and 65 had induced labor. Only 5 patients had elective LSCS out of 180 for the indications like cephalopelvic disproportion, previous LSCS, and fibroid with pregnancy. The correlation of type of onset labor with corrected fetal adrenal gland was assessed and it was found that there exists a significant difference in both right and left corrected fetal adrenal gland volume between term and preterm labor cases with a p-value of <0.0001*. Interestingly, the mean value of corrected fetal adrenal gland volume was maximum in spontaneous preterm labor cases compared to term spontaneous labor cases. Our findings are much similar to other studies; Guler et al also reported higher value of FZD/TGD ratio was in preterm birth group, compared to the term birth group. Likewise, Guler et al and Bhat et al also reported a significant association of corrected fetal adrenal gland volume (cFAGV) with spontaneous onset labor and recommended that cFAGV is the efficient and precise marker to predict the spontaneous onset labor. In the present study, we observed that out of 175 non elective-LSCS cases, (72%) subjects had normal vaginal delivery, (2.29%) had instrumental vaginal delivery, and (25.71%) had emergency caesarean delivery for fetal distress, non- progress of labor, malpresentation and previous LSCS in labour. We analyzed the association of right and left adrenal gland volume with mode of delivery and APGAR score (<7 and ≥7) and found that the difference is statistically insignificant in both the cases. Turan et al reported a significant association of premature onset labor with fetal adrenal gland enlargement, which in turn affects the mode of delivery in a way whether delivery occurred before or after the onset labor.

CONCLUSION

With this study it is concluded that the corrected fetal adrenal gland volume is a predictor for onset of labor (term or preterm). At term, the cFAGV is <628mm³/kg and at preterm the cFAGV is >628 mm³/kg. The neonatologist thus can be fore warned about the preterm delivery or if the hospital has limited resources the patient with fetus in utero can be referred to higher center, but larger multicentric studies are required to formulate the guidelines for the same and its inclusion in the routine screening of the antenatal women.

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