ULTRASOUND ASSESSMENT OF FETAL ADRENAL GLAND VOLUME (FAGV) AND ADRENAL FETAL ZONE ENLARGEMENT(AFZE):VIABLE AND SUPERIOR ALTERNATIVES TO CERVICAL LENGTH (CL) IN ACCURATE PREDICTION OF PRETERM BIRTHS.

Radiodiagnosis

Jatin Venugopal Kutnikar*	MBBS, Junior resident in MD (Radiodiagnosis) Dept. of Radiodiagnosis, Sree Balaji Medical College and Hospital, 7 Works Road, Chromepet, Chennai, IN 600044. *Corresponding Author
Saravanan Kannan	MBBS, MD, Associate Professor, Dept. of Radiodiagnosis, Sree Balaji Medical College and Hospital, 7 Works Road, Chromepet, Chennai, IN 600044.
Prabhakaran Maduraimuthu	B.Sc., MBBS, DMRD, MD, Professor and Head of Department, Dept. of Radiodiagnosis, Sree Balaji Medical College and Hospital, 7 Works Road, Chromepet, Chennai, IN 600044.

ABSTRACT

Background: Owing to associated neonatal death, morbidity and impairment in later life, preterm birth is a major public health issue. Pregnant ladies presenting to the antenatal clinic were recruited in order to predict spontaneous preterm births bythe novel method of assessing the Fetal Adrenal Gland Volume (FAGV) and Adrenal Fetal ZoneEnlargement(AFZE) and comparing it with Cervical length.

Material And Methods: This was a prospective observational study done at a tertiary hospital in Chennai.The formulae,AFZE=Gland length/Central fetal zone length and FAGV=0.523 x length x width x depth. cFAGV=fetal adrenal gland volume/estimated fetal weight =FAGV/EFW, were employed for the purpose of this study. 2 or Fisher's exact tests,Mann-Whitney or student-t test were calculated for appropriate variables.
Pregnant women with uncomplicated pregnancy with gestational age between 21-34 weeks were recruited for this study.

Results:70 pregnant women were studied from May2019 to August 2020 and had an average age of 25 years and mean age of gestation being 27.1 weeks.26(37.1%) of these had a preterm delivery of ≤7 days.AFZE emerged as the best predictor among the three metrics with sensitivity of 100% and specificity of ~90 %.cFAGV showed ~80%/~89% sensitivity and specificity.This was in contrast to cervical length of ≤16 mm having just 55% and 60% sensitivity and specificity respectively.

Summary:USG estimation of AFZE and cFAGV are more reliable and accurate indicators than CL for spontaneous preterm delivery and can be used in the routine scanning of patients with early symptoms of preterm labour to plan the management more effectively.

KEYWORDS

Fetal Adrenal Gland Volume; Adrenal Fetal Zone Enlargement; Cervical Length; Antenatal Ultrasound; Preterm birth

INTRODUCTION:

Preterm birth(premature birth)is a major public health issue around the globe due to associated neonatal(first twenty eight days of life)mortality and short-and long-term disability causation in later life.The World Health Organization(WHO)describes preterm as babies born alive prior to 37 completed weeks of gestation or less than 259 days of gestation after the first day of the last menstrual period(LMP) of a woman.Normally,a pregnancy lasts about 40 weeks. Statistics show that 1,50,00,000 babies each year have a premature delivery, which is about one in every 10 births worldwide.

Each year,almost 10,00,000 children die as a result of complications of preterm birth(2013). The preterm birth rate varies from 5 per cent to 18 per cent of babies born in 184 countries.In India,out of 2.7 crore babies born every year(2010 data),35 lakh babies born are premature.

Recently intervention techniques including use of progesterone and cervical cerclage procedure have shown a decrease in the preterm birth rate among at risk women.[1-6]

"Placental clock"Plays a major role in the interruption of uterine quiescence-leads to cascade of events-onset of labor.[7,8]Placental corticotrophin-releasing hormone(CRH)is the main mediator of placental clock.It activates(and causes enlargement)of the fetal adrenal gland(increase is mainly due to considerable enlargement of the central fetal zone).

The assessment of size/volume of fetal adrenal gland could be employed in the assessment of spontaneous-preterm births.This concept has been investigated and found useful in predicting preterm labor.[9,10]

OBJECTIVE:
1. To determine an imaging method to predict spontaneous preterm labor that satisfies the following:
- High degree of sensitivity and specificity.
- Inexpensive.
- Widely available.
- Non-invasive.
- Can be an easy add on to the existing regular prenatal evaluation methods.

2. Review of literature available on the existing method (cervical length assessment).

3. Evaluation of Ultrasound assessment of fetal adrenal gland volume(FAGV)and adrenal fetal zone enlargement(AFZE)as a viable and Superior alternatives to Cervical Length(CL)in accurate prediction of Preterm Births.

4. To assess the sensitivity and specificity of the above parameters for the accurate prediction of Preterm Births.

MATERIALS AND METHODS:
This was a prospective observational study performed at Department of Radiodiagnosis,Sree Balaji Medical College and Hospital,Chennai

Study Duration-May 2019 to August 2020.
- Patients presenting to antenatal clinic with were recruited for the study and were assessed with 2-D ultrasound to measure FAGV, AFZE and CL.
- Ultrasound modality was employed for the assessment using the curvilinear and Transvaginal high frequency probe.
- To avoid the bias, all patients were imaged by a single sonographer blinded to the outcome of the pregnancy.
- The interval (days) was computed from 2D ultrasound examination to delivery of the fetus, and delivery outcomes were recorded.
- Gestational age (GA) was established based on the last menstrual period(LMP) or based on an ultrasound evaluation prior to 20 weeks(preferable).

Inclusion Criteria:
- Singleton pregnancies who present with symptoms relating to preterm labor or preterm premature rupture of membranes (PPROM).
- Between 21 and 34 weeks.
- Consenting patient.
- PPROM-confirmed by visualizing amniotic fluid vaginal pooling

at the time of the sterile speculum examination.
- Positivity of the nitrazine test and ferning tests were also considered diagnostic.

Exclusion Criteria:
- Suspected fetal growth restriction(sonographically estimated fetal weight 10th percentile),
- Maternal medical conditions(e.g.,hypertension, preeclampsia, diabetes, or thyroid or adrenal diseases),and
- Presence of fetal heart rate abnormalities at enrolment (i.e.,bradycardia or prolonged variable decelerations).
- Patient attrition.

Cervical Length (CL):
- Traditionally,2-dimensional(2D) ultrasound measurement of cervical length(CL) is employed to identify at-risk women for PTB and is now used as a widespread tool for risk assessment.[11]
- **Cervical length** is less than 25 mm before 28 weeks may be indicative of preterm birth.[12]
- Main drawback-cervical shortening is observed in many pregnant females who have a normal term births and as such is non-specific for evaluating PTB.

Alternative-
Ultrasound Assessment Of Fetal Adrenal Gland Volume(fagv) And Adrenal Fetal Zone Enlargement(AFZE).(figure 1)
- The fetal adrenal zone(AFZ) is imaged as hyperechoic centre in the fetal adrenal gland.
- The depth and width of the fetal adrenal zone to be noted in the transverse plane.
- The right fetal adrenal gland to be imaged,as it can be better visualized,compared to left adrenal gland (commonly obscured due to rib shadowing).
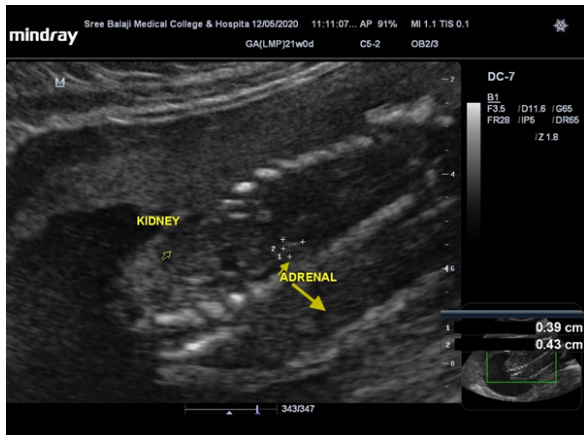
Figure 1: Ultrasound Imaging Of Right Fetal Adrenal Gland.

Statistical Analysis:
Adrenal fetal zone enlargement (AFZE)=

Fetal adrenal gland volume (FAGV) = (0.523 x length x width x depth).

Corrected fetal adrenal gland volume

$$(cFAGV)= \frac{Gland\ length}{Central\ fetal\ zone\ length} = \frac{L}{l}$$

Data collected was tabulated in Microsoft ® Excel 2019,SPSS 16 and Med-calc.
- Demog$\frac{Fetal\ adrenal\ gland\ volume}{Estimated\ fetal\ weight} = \frac{FAGV}{EFW}$ neans.
- Catego   ing   2 or Fisher's exact tests as
- Continuous variables were analysed using Mann-Whitney or student t test according to their distributions.
- Graphical representation of the results.

RESULTS:
70 pregnant women between 21 to 34 weeks were studied from May 2019 to August 2020.

- Demographic data is represented in Table 1.
- 26(37.1%) of these had a preterm delivery of ≤7 days.

- AFZE emerged as the best predictor among the three metrics with sensitivity of 100% and specificity of ~90 %.
- cFAGV showed ~80%/~89% sensitivity and specificity.
- CL showed ~55%/60% sensitivity and specificity.
- All figures were statistically significant(p<0.01).(Table-2)

Table 1: Demographic Data

Characteristics	All cases (n=70)	Delivery ≤7 days (n=26)	Delivery ≥ 7 days (n=44)	p value
Demographic				
Age y, mean (SD)	25 (6.1)	23.5 (5.7)	25.8 (6.4)	NS
Parity, median (range)	1 (0-3)	0 (0-3)	1 (0-3)	NS
Gestational age at enrolment, wks., mean (SD)	27.1 (3.2)	27.2 (3.5)	27 (3.3)	NS
Presence of PPROM, n (%)	14 (20)	8 (30.7)	6 (13.6)	NS
Outcome				
Gestational age at delivery, wks., mean (SD)	33 (4.5)	29 (3.3)	35 (3.8)	<0.01
Delivery weight, g, Mean (SD)	1801 (860)	1205 (501)	2298 (772)	<0.01
Caesarean section, n(%)	20 (28.6)	9 (34.6)	11 (25.0)	NS
Delivery <37 weeks, n (%)	55 (78.5)	25 (96.2)	30 (68.2)	NS
Delivery <34 weeks, n (%)	42 (60)	23 (88.4)	19 (43.2)	<0.01

NS, not significant; PPROM, preterm premature rupture of membranes.

Table 2:comparision Of Ultrasound Examination Findings According To Delivery Interval

Variable	Delivery ≤7 days (n=26)	Delivery ≥ 7 days (n=44)	p value
Cervical length, mm, mean (SD)	17.4 (10.1)	16.8 (12.1)	NS
Corrected adrenal gland volume, mm3/kg, mean (SD)	565.5 (220)	332(127.1)	<0.01
Fetal zone enlargement, %, mean (SD)	60 (7.0)	40 (10.2)	<0.01
Variable	Sensitivity (95% CI)	Specificity (95% CI)	
Cervical length ≤16 mm	55%	60%	
Corrected adrenal gland volume ≥420 mm3/kg	80%	89%	
Fetal zone enlargement ≥49.7%	100%	90%	

NS- not significant.
CI, confidence interval

Implications:
Ultrasound estimation of AFZE and cFAGV are more reliable and accurate indicators than CL for spontaneous preterm delivery of ≤7 days and can be used in the routine scanning of patients with early symptoms of preterm labour to plan the management more effectively. 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.13 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. 14

Using a combination of the above predictors to get the best equilibrium of sensitivity and specificity is desirable.

It is now understood that the changes of the adrenal gland occur over a shorter duration and the value of the adrenal gland measurement is only as an acute (within 5-7 days) marker of spontaneous preterm birth rather than an early marker, such as cervical length.15

It is important to note that the levels of maternal estriol produced primarily by the foetal adrenal gland were documented to increase approximately 4 weeks before preterm birth.16,17

In addition, other investigators have found that maternal cortico-releasing hormone levels (a proxy marker of fetal adrenal size) in women who proceed to have preterm births start to increase at 16 to 20 weeks.18

Future Prospects:
The need to study larger populations, different ethnic groups and other variables.

The determination of day-wise predictable cut offs giving fetal adrenal glands a new position in the prediction of labor (term or preterm) in modern obstetrics.

Clarity of plan for the obstetrician to plan the next course of treatment and, parturient mother and her family time to plan accordingly.

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