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Research Article

Assessment of fetal adrenal gland enlargement in term and preterm labor cases

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ABSTRACT

Background: The objective of this study was to compare the Fetal Zone Depth (FZD) of fetal adrenal gland in term and preterm labor cases.
Methods: Twenty nine preterm pregnant women at 29-36 weeks of gestation with single pregnancy admitted with the clinical diagnosis of preterm labor and the comparison group of 33 pregnant women at 37-40 weeks with term pregnancy were included in this study. FZD and Total Gland Depth (TGD) of fetal adrenal gland of the entire fetuses in sagittal plane were ultrasonographically measured and FZD/TGD ratios were calculated. Demographic and clinical features, laboratory findings and fetal adrenal gland FZD/TGD ratios were compared between the two groups.
Results: No difference was found between the two groups in respect of age, number of pregnancies and delivery method (P >0.05); yet preterm birth history and duration of hospital stay 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 (55.4% ± 4.9 vs. 47.7% ± 5.6; P <0.001).
Conclusion: The growth in FZ as a fetal adaptation mechanism in increased fetal stress in preterm labor cases was at a significant level. Once supported by more comprehensive studies, we think that this result would be beneficial in the prediction of preterm labor in clinical practice.

Keywords: Preterm labor, Adrenal gland, Fetal zone, Ultrasonography

INTRODUCTION

Despite medical progresses, preterm birth retains its actuality in modern obstetrics and remains the leading cause of perinatal morbidity and mortality. The incidence of preterm birth is 10% in the entire deliveries.[1] It is stressed that severe mortality and morbidity occur in the deliveries before 34th week of gestation.[2] When neonatal mortality rates are reviewed, we have observed that 83% of these rates correspond to the babies born before the completion of 37th week of pregnancy.[3]

Approximately 20-30% of the preterm births (i.e. 1-4% of all births) are caused by medical and obstetric reasons; while 70-80% of these births may be linked to spontaneous idiopathic reasons associated or not associated with premature rupture of membranes (PROM).[4] Preeclampsia, fetal distress, Fetal Growth Retardation (FGR), abruption placenta and fetal death may be referred to as the medical and obstetric causes.[5] The prediction and prevention of preterm births are among the major issues of obstetrics. Prediction and prevention of preterm births by determining the risk

factors would be the most appropriate approach with a view to reduce the preterm birth rates. Risk scoring systems, digital examination of the cervix, biochemical markers, ultrasonographic cervical length measurement are the methods used in predicting preterm labor.[6,7] Currently, ultrasonographic cervical length measurement is the most frequently used method in clinical practice for the prediction of preterm labor.[8,9]

Fetal adrenal gland is comprised of 4 zones at fetal life. These zones are: - from inner to outer zones - "Fetal Zone" (FZ), "Transitional Zone" (TZ), "Definitive Zone" (DZ) or neocortex and finally "fetal adrenal capsule" (C).[10,11] The response of the layers forming fetal adrenal gland to the hypothalamic-pituitary-axis may vary depending on the gestational week and cellular reconstruction. The activation of the fetal hypothalamicpituitary-adrenal axis as well as the discussion regarding the variety of placental and fetal adrenal gland endocrine signaling pathways are crucial in respect of launching the process of normal parturition.[12] It is known that the increased dehydroepinadrosterone-sulfate (DHEAS) production in the central zone of the fetal adrenal gland (i.e. fetal zone) is caused by biochemical activation. In this manner, we observe a dimensional increase in the whole fetal adrenal gland which mostly emanates from the remarkable enlargement of the central fetal zone.[13]

An autopsy study provides the arguments in favor of such process. According to this study, the newborns delivered in the setting of idiopathic PTB had significantly higher adrenal gland weight compared to those that have delivered secondary to fetal/maternal hemorrhage.[14] The recent studies conducted in this context have revealed that the ultrasound-measured fetal adrenal gland volume is highly predictive of preterm birth, independent of expected birth weight and gestational week.[15,16] Hence, this study aims at comparing the fetal adrenal gland FZD/TGD ratios in preterm and term labor through ultrasonographic assessment.

METHODS

Twenty nine preterm pregnant women at 29-36 weeks of gestation with single pregnancy admitted to the obstetrics clinic of a tertiary hospital with the clinical diagnosis of preterm labor. On the other hand, a comparison group of 33 pregnant women between 37 and 40 weeks with term pregnancy was included in this study. Before the study, the written consent form was received from the hospitals following the reception of the required approval of the ethics committee of the hospital. Placenta previa, diabetes mellitus, gestational diabetes, maternal heart disease, preeclampsia-eclampsia, chronic hypertension, abruption placenta, multiple pregnancies, polyhydramnios, oligohydramnios, existence of anemia, acute pyretic disease, fetal distress, FGR, stillborn fetuses, fetal abnormality incompatible with life were specified as exclusion criteria for participation in the study.

In the diagnosis of preterm labor, the existence of regular, effective (45-50 mmHg) uterine contractions, 4 in 20 minutes or 6 in 60 minutes; and cervical dilatation of ≥2 cm or the existence of a cervical change during observations were considered as criteria. The pregnant women, whose amniorexis and premature rupture of membranes were detected through sterile speculum examination, were considered preterm labor regardless of the existence of contractions.

The entire pregnant women undergoing systemic and obstetric examination were initially assessed by routine transabdominal ultrasonography (3.5 MHz convex abdominal prob, Siemens Acuson Antares®). During ultrasonography, fetal biometric measurements were performed; fetal weight has been calculated and the relevant gestational ages were verified. Fetal adrenal gland was assessed. Early term pregnancy ultrasonographies were used to detect the week of gestation of those who do not know their last menstrual periods. This was followed by the ultrasonographic cervical assessment of the patients in the lithotomy position with an empty bladder (7.5 MHz convex vaginal prob, Siemens Acuson Antares®). Ultrasonographic technical assessment of the entire pregnant women was conducted by the same physician to ensure standardization. The age, existing internal diseases, gravida, parity, preterm labor history, blood group, rhesus isoimmunization of the patients were queried and recorded. Following the completion of the delivery, delivery method, duration of hospital stay, gestational age, birth weight and gender of the newborn, antepartum and postpartum maternal hemoglobin levels, presence of any tocolitic treatment were recorded.

The fetal adrenal gland was assessed by means of abdominal probe passing from the transverse plane, where fetal renal structures are observed, to the sagittal plane at a 90 degrees angle. Hyperechogenic central portion of the fetal adrenal gland in the sagittal plane, Fetal Zone Depth (FZD) in anterior-posterior plane, and Total Gland Depth (TGD) in the same plane were measured in millimeters. The FZD/TGD ratio has helped us to obtain the data underlying our study (Figure 1). Considering the anatomic structures, we observed that the right adrenal gland has triangular, tetrahedral, "V" or "Y" multiple variations; while the left adrenal gland was mostly semilunar-shaped. Hence, the left fetal adrenal gland was studied with a view to ensure standardization during the assessment.

During cervical assessment, the transvaginal probe was slowly advanced into the vagina and the sagittal view of the cervix was obtained by being attentive to avoid any potential pressure on the cervix. Cervical measurements were performed at the synchronous cross sectional images of internal os, external os, cervical canal and endocervical mucosa and by an enlargement in a way to cover ¾ of the screen. Furthermore, if the distance between internal os and external os was not on a single

line, it was measured based on the piecewise linear method and the total cervical length was obtained by the addition of these pieces.

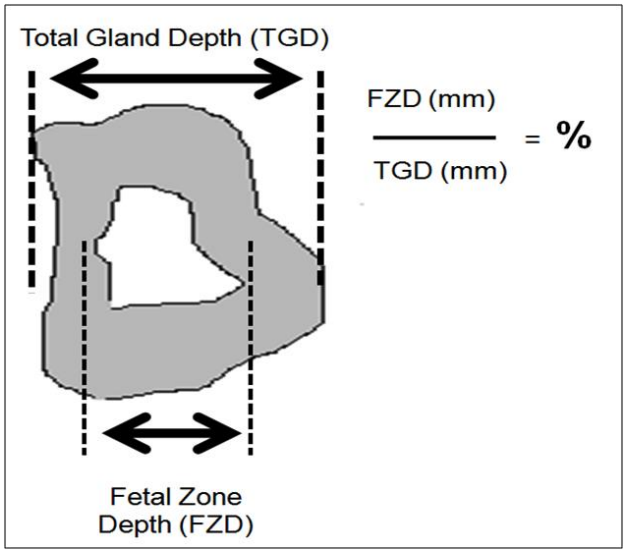

Figure 1: Measurement of fetal zone depth and total gland depth: a) Schematization of FZD and TGD measuring technique. FZD/TGD ratio: b) Sonographic schematization of FZD and TGD measuring technique (demonstration from preterm labor group). FZD/TGD: fetal zone depth/total gland depth.

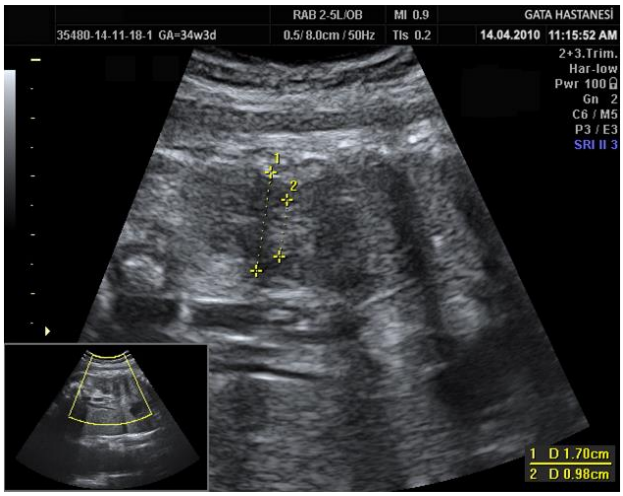

Figure 2: Ultrasonographic technical assessment of the entire pregnant women was conducted by the same physician to ensure standardization.

Data analyses were performed using SPSS version 15.0 for Windows. Parametric variables were compared using Student's t-test; whereas nonparametric variables were compared by the Mann-Whitney U-test. Differences between the groups were assessed using a χ^2 test and Fisher's exact test for categorical variables. A P value <0.05 was considered statistically significant.

RESULTS

Totally 62 pregnant women were included in the study. Two assessment groups covering 29 (46.7%) preterm and 33 (53.3%) term cases as a comparison group were created. Preterm birth taken place between 29-36th weeks (average 33.8 ± 1.8) while term births taken place between 38-41st weeks (average 39.1 ± 0.7) (Table 1).

No statistically significant difference was detected between the two groups in respect of age, number of pregnancies, delivery method, maternal hemoglobin levels and genders of the new born (P >0.05).

However, the number of deliveries and weight of the newborn were higher in the term group; while preterm labor history and duration of hospital stay were higher in the preterm group (P <0.05) (Table 1).

Table 1: Demographic characteristics of the groups.

Demographic characteristics	Preterm group (n=29)	Term group (n=33)	P
Age	30.6±5.4	30.1±4.0	0.72
Gravidity	1.6±0.9	2.0±0.7	0.10
Parity	1.3±0.5	1.8±0.6	<0.001
Preterm labor history*			
No	25 (86)	33 (100)	0.02
Yes	4 (14)	-	
Hemoglobin (g/dl)	12.2±1.4	12.3±1.0	0.60
Duration of hospital stay (day)	2.3±2.8	1.1±0.4	0.03
Labor time	33.8±1.8	39.1±0.7	<0.001
Delivery method*			
Vaginal	27 (93)	33 (100)	0.21
Abdominal	2 (7)	-	
Weight of new-born (gram)	2350.6±544.9	3378.4±466.3	<0.001
Fetal sex*			
Male	16 (55)	17 (52)	0.77
Female	13 (45)	16 (48)	

*Data are given as n (%); the other data are given as mean ± SD; g/dl: gram/deciliter

No statistically significant difference could be detected between the two groups in respect of cervical measurements (P = 0.27) (Table 2). In the preterm birth case, FZD/TGD ratio was statistically significantly higher in the preterm birth, compared to the term births (55.4% ± 4.9 vs. 47.7% ± 5.6) (P <0.001).

Figure 3 displays the weekly distribution of the FZD/TGD ratio for both groups.

Table 2: Comparison of cervical length and FZD/TGD ratio.

Sonographic findings	Preterm group (n=29)	Term group (n=33)	P
Cervical length (mm)	14.5±9.2	17.2±9.5	0.27
FZD/TGD (%)	55.4±4.9	47.7±5.6	<0.001

Data are given as mean ± SD; mm: millimeter; FZD/TGD: fetal zone depth/total gland depth

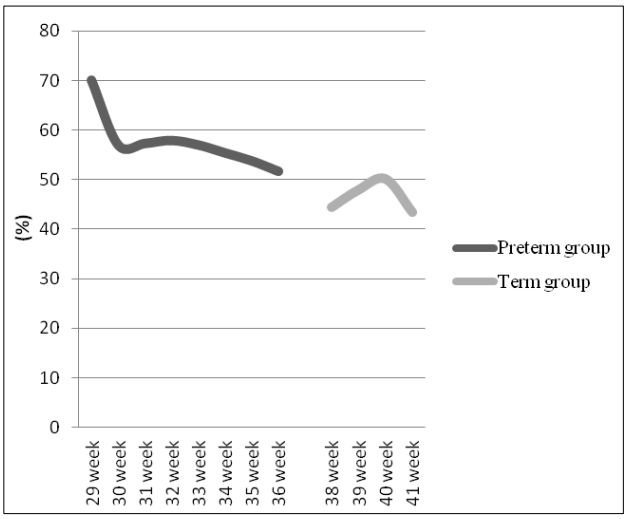

Figure 3: Week by week FZD/TGD ratio distribution curve. FZD/TGD: fetal zone depth/total gland depth.

DISCUSSION

Despite the remarkable developments in the prognosis of the low birth weight (LWB, <2500 gram) babies due to the recent progresses in the newborn care, there is no decline in the preterm birth rates. The rates of neonatal and postnatal deaths decreased by half during the last two decades. However, the mortality rates did not decline for preterm (<37 week) births and LWB babies.[17] For that reason, determination of high risk group for preterm birth; examining our patient follow-up and treatment policies and prevention of preterm births and their complications are issues of great importance for the obstetrician.

Reliable and incomplete results used for the prediction of preterm birth or the management of follow-up-treatment regimens led to the structuring of various studies for cervical length assessment purposes. The common result in such studies is that the substantial shortening of cervical length poses a risk for preterm patient, irrespective of whether the patient is multiparous or nulliparous.[8,9,18] Cervical length measurement is an inevitable part of our clinical practice due to the widespread use of ultrasonography and easiness of assessment. As a result of the vaginal sonographic assessment we found out the cervical length measurements of the two groups were not different. This is linked to the application of the patient population for admission to the clinics at the later stages of labor.

The studies conducted for long years focused on the assessment of maternal responses of the maternal mechanisms held responsible for the etiology of premature labor. However, in clinical cases like preterm labor with raised fetal stress, the assessment of clinical results of hypothalamic-pituitary-adrenal axis, hormonal structures perpetuating this axis and this hormone stimulation recently become important. The focal point of this study, FZ of the fetal adrenal gland produces the precursors of the steroid hormones transforming into estrogen and other cortisol derivatives in the placenta. Fetal cortisol increases placental Corticotropin-Releasing Hormone (CRH) and causes the release of PGE2 and PGF2α of the placental endogenous birth labor different than the pituitary corticotropin releasing hormone. Considering the site of cortisol production reaching maximum levels in circulating maternal blood at 34-36th weeks of pregnancy under the rules of adaptation to fetal stress with estrogen; one will see that the increase in FZ width of the preterm cases is an expected result.[19,20]

Buhimschi et al. assessed the corrected fetal adrenal gland volume and cortisol to DHEAS ratios for the cases where elevated inflammation levels cause preterm birth. They found out that, in 51 cases justifying intraamniotic infection by amniocentesis, the higher corrected fetal adrenal gland volume is correlated with increased IL-6 levels and reduced cortisol to DHEAS ratios. As a result of the study, the corrected fetal gland volume is accepted as a reflection of an intrauterine adaptation process in infection and preterm labor cases with increased fetal stress.[21] In their assessment of fetal adrenal gland in high risk pregnancies, Ljubitsh et al. obtained normal levels for fetal adrenal gland measurements out of 131 cases without gestational diabetes (GDM) or hypertension, and compared this control group with 82 cases with GDM and hypertension. The study showed an increase in fetal adrenal gland measurements compared to normal population, in cases of GDM; while lower limits of normal were obtained at adrenal gland measurements of hypertensive cases.[22]

On the other hand, in the study conducted by Turan et al. measuring the fetal adrenal gland volume in the risky group as an unusual method for preterm labor; fetal adrenal gland volumes of the deliveries before 37th week, as an indicator of hypothalamic-pituitary-adrenal functioning, were assessed by three-dimensional ultrasonography. Fifty three patients with preterm labor symptoms and 73 cases without symptoms were included in this study. Corrected adrenal gland volume for estimated fetal weight was measured and 422 mm^3/kg was set as limit value. The probability of delivery within 5 days of the cases exceeding this value was statistically significant.[15] In another study of the same group, corrected adrenal gland volume for estimated fetal

weight, fetal zone enlargement of adrenal gland and cervical length were assessed by two and three-dimensional ultrasonography. The ratio between whole gland depth and central fetal zone depth, vaginal ultrasound assessment of cervical length data, specificity and sensitivity of prediction of preterm labor of corrected fetal adrenal gland volume measurements within 7 days, were elaborated here, as in our study. As a result of 7-day follow-up of fetal zone enlargement independent from obstetrical history and tocolytic treatment, specificity and sensitivity levels are higher compared to the other two methods in respect of ending in preterm labor.[16]

In this study, we compared 29 preterm labor cases with 33 cases of spontaneous delivery at term. Though they seem to be the same in respect of mechanism and fetal response, preterm and term labors are actually far from being similar particularly when we consider the anatomical responses to hormonal effects like increment in depth of fetal adrenal gland. FZD/TGD ratio was higher in preterm birth group, compared to the term birth group (P <0.001). Examining the entire risk factors of preterm labor, all the reasons except for maternal age and ethnic origin contribute to the environment of a difficult intrauterine fetal growth and development. While this environment implies a mechanism of severe stress adaptation, the lack of such features in a term fetus accounts for the difference between the two comparison groups.

The results obtained in our study propound that the ultrasonographic assessment of fetal adrenal gland and fetal zone enlargement may be beneficial for the cases presented with preterm labor symptoms. We think that these assessment results may provide rapid administration and treatment facilities with real indications for the patient groups admitted with preterm labor symptoms. For instance, one may encounter the fact of the implementation of unnecessary treatments as cerclage, tocolysis and steroids in cases of increased fetal zone enlargement. Regarding the topic of fetal adrenal gland on which new researches are conducted in the medical literature, numerous studies are needed for setting limit values of fetal zone enlargement, assessing other high risk pregnancies and making serious changes in our follow-up and treatment protocols.

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Ethical approval: The study was approved by the hospital ethics committee

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