ORIGINAL ARTICLE

FETAL ADRENAL GLAND SIZE AND PREDICTION OF PRETERM BIRTH

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ABSTRACT

Objective: To assess whether ultrasound-measured fetal adrenal gland size in symptomatic women is effective in predicting spontaneous preterm delivery within 7 days and to compare these predictions with the cervical length measurement. Methods: We performed a prospective study with 49 pregnant women who showed symptoms of spontaneous preterm birth between 24-36 weeks of gestation and 60 women with normal pregnancies. Fetal adrenal glands were measured by ultrasonography and compared between the two groups. Also, an ultrasound exam was performed to obtain the cervical length measurement on day 1 of hospital admission. The main outcome measure was the time between the ultrasound exam and delivery, which was classified into two groups: delivery ≤7 days and delivery >7 days. Results: The fetal adrenal gland biometry predicted delivery within 7 days in pregnant women with symptoms of spontaneous preterm birth and had a predictive accuracy better than cervical length measurement. (ROC curve 0.701 versus 0.640. Conclusion: This study concludes that fetal adrenal gland measurements can be used as a noninvasive and cost effective anew marker in prediction of preterm birth.

KEYWORDS: *Preterm birth, adrenal gland, ultrasound*

INTRODUCTION

Preterm delivery (<37 weeks) still remains the biggest cause of perinatal morbidity and mortality in developed countries [1]. Preterm birth complicates 12% of pregnancies and approximately 50% of all pregnant women deliver their child prior to 37 weeks of gestation [2]. Although risk factors for preterm birth, such as multiple gestations, uterine anomalies, prior preterm birth, extremes of maternal age, and low maternal pregnancy BMI (Body Mass Index), are known, relying solely on these factors will fail to predict at least 50% of spontaneous preterm birth [3]. Unfortunately, we still lack accurate predictors of preterm delivery [4]. The American College of Obstetricians and Gynecologists (ACOG) recommends two tests for the prediction of preterm birth: cervical length and fibronectin test. Cervical length measurement has been accepted as the most accurate ultrasound predictive marker for spontaneous preterm birth in both low- and high-risk pregnant women [5], [6]. The fetal adrenal glands play an important role in in the maintenance of pregnancy and the initiation of labor [7]. Necropsy examination of

preterm fetuses found that fetal adrenal gland weight was significantly higher for those fetuses undergoing spontaneous preterm birth compared to those delivered for maternal reasons [8].

The fetal hypothalamic–pituitary–adrenal axis has a strong influence on placental hormone production, including those critical to the initiation of labor. The fetal adrenal gland produces dehydroepiandrosterone sulfate, which gets converted to dehydroepiandrosterone (DHEA) and aromatized in the placenta to estradiol and then estriol, which, in turn, are transferred to the maternal circulation to participate in the initiation of parturition [9]. Elevated maternal estriol levels have been shown to correlate with delivery before 37 weeks [10]. The fetal adrenal gland also produces cortisol, which acts in the placenta to promote oxytocin and prostaglandin production, activating uterine contractions and cervical change [9]. Fetal cortisol promotes corticotropin-releasing hormone synthesis by the placenta, resulting in a positive-feedback loop increasing fetal production of cortisol. Abnormal or premature rises in corticotropin-releasing hormone (CRH) have been associated with preterm birth [11], [12], [13], and fetal adrenal hyperplasia has been reported in association with preterm birth [8].

It has been demonstrated that women with symptoms of preterm labor have larger fetal adrenal glands than asymptomatic woman. Further, among women presenting with symptoms of preterm labor, those who delivered within 5–7 days had significantly larger fetal adrenal gland volumes than those who delivery later than 7 days [14], [15]. Given the need to develop screening tools to identify women at risk of preterm delivery, we conducted a prospective study to determine whether measurement of adrenal gland volume could predict spontaneous preterm birth and to compare this prediction with cervical length.

MATERIAL AND METHODS

We conducted a prospective study in Saint Pantelimon Hospital, between January 2021 and January 2022, with pregnant women between 24 and 36 weeks of gestation presenting with signs or symptoms of preterm labor.

The study was approved by the Ethical Committee and all participants provided informed consent. Enrollment criteria were: singleton fetus, abdominal pain with uterine contractions, modifications of the uterine cervix, and the necessity of tocolytic medication. The exclusion criteria were: fetal malformations, pre-gestational or gestational diabetes mellitus, chronic arterial hypertension, pre-eclampsia, fetal growth restriction, endocrine diseases, amniotic fluid disorders, use of progesterone. Gestational age was calculated based on the last menstrual period and ultrasonographic examination before 20 weeks. The ultrasound exams were performed at admission using a Voluson S10 apparatus. The assessments of cervical length were performed using the transvaginal route, according to Fetal Medicine Foundation guidelines: a transvaginal probe was introduced to the middle third of the vagina, and three measurements were made [16]. The cutoff of cervical length measurement was 20 mm. All pregnant women with spontaneous preterm birth risk received tocolytic medication for at least 24 h, and dexamethasone until fetal pulmonary maturation. The fetal adrenal gland was assessed at admission, we measured total gland length, total gland width, and fetal zone width in a 2-dimensional transverse plane (Figure 1). Above the kidneys, the fetal adrenal gland appears as inverted V Shaped structure. Was measured only the right fetal adrenal gland, as it is better visualized than left fetal adrenal gland which obscured by the rib shadow.

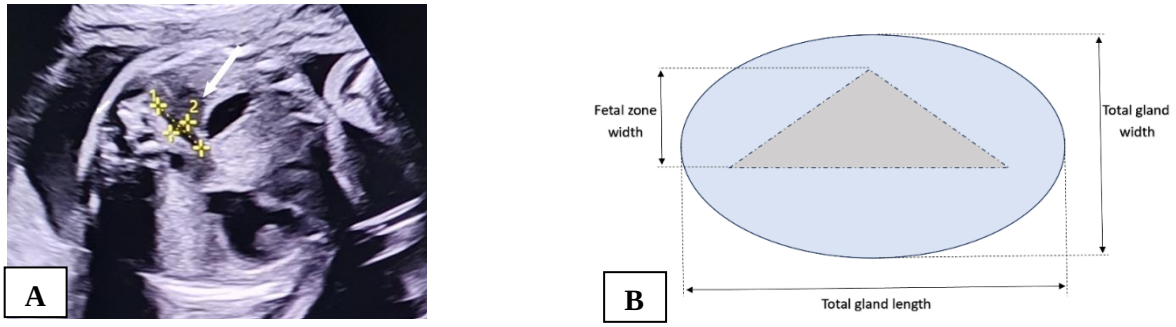

Figure 1 – A. 2D ultrasound plane, abdominal circumference plane. The arrow shows the right adrenal gland. B. Schematic of fetal adrenal gland measurements

RESULTS

In our group, the majority were young women with low parity (85.72%). Additionally, 87.75% of those who gave birth within seven days of the ultrasound had a history of previous preterm birth. The features of the studied population are presented in Table 1, which displays maternal characteristics and perinatal outcomes for both groups (delivery within ≤7 days and delivery after >7 days), without considering statistical differences between the groups. Table 2 presents the characteristics of the patients regarding uterine cervix measurement and ultrasonographic outcomes corresponding to both groups (delivery ≤7 days and delivery >7 days). As can be seen, we found a larger adrenal gland in women who gave birth within 7 days.

Characteristics	All cases	Delivery ≤7 days	Delivery >7 days	*p*
Maternal age (Mean ± SD)	28.78 ± 7.75	29.40 ±7.72	24.33 ±7.03	0.283
Gestational age (Mean ± SD)	31.86 ± 2.93	31.74 ±3.05	32.67 ±1.86	0.126
Previous prematurity, n (%)	49 (100%)	43 (87.8%)	6 (12.2%)	0.834
Yes	5 (100%)	5 (100%)	0 (0%)	
No	44 (100%)	38 (86.4%)	6 (13.6%)	
Birth weight	1852.45 ± 564.56	1821.63 ±556.96	2073.33 ±622.31	<0.001
Type of delivery	49 (100%)	43 (87.8%)	6 (12.2%)	
Cesarean section	41 (100%)	35 (85.4%)	6 (14.6%)	
Vaginal	8 (100%)	8 (100%)	0 (0%)	

Table 1 – Distribution of maternal characteristics depending on timing of delivery

Ultrasound findings	All cases	Delivery ≤7 days	Delivery >7 days	*p*
Cervical length measurement, n (%)	49 (100%)	43 (87.8%)	6 (12.2%)	0.641
< 20 mm	12 (100%)	12 (100%)	0 (0%)	
≥ 20 mm	37 (100%)	31 (83.8%)	6 (16.2%)	
Total length adrenal gland (Mean ± SD)	25.36 ± 3.79	25.65 ± 3.77	23.05 ± 3.36	<0.001
Total width adrenal gland (Mean ± SD)	12.55 ± 1.92	12.70 ± 1.94	11.51 ± 1.53	
Fetal width adrenal gland (Mean ± SD)	6.27 ± 1.03	6.36 ± 0.99	5.62 ± 1.11	

Table 2 – Distribution of uterine cervix measurement and ultrasonographic outcomes according to the delivery period.

Figure 1 displays the analysis of the ROC (Receiver Operator Characteristic) curve for the total length of adrenal gland measurement considering an 87.8% prevalence of delivery within 7 days. The area under the ROC curve, is 0.700 (95% confidence interval 0.488–0.911) (p = 0.064), value considered acceptable. The best obtained cutoff for the total length of adrenal gland measurement is 24.5 mm. The ROC curve analysis has been performed for the cervix length measurement under 20 mm and obtained an area under the ROC curve of 0.640, with a 95% confidence interval 0.572–0.707 (p < 0.001).

Figure 2 reveals the results of the ROC curve analysis for the fetal width of adrenal gland measurement considering 88% prevalence of delivery within 7 days. The ROC curve is 0.702 (95% confidence interval 0.525–0.878) (p= 0.025). The best obtained cutoff for the total width of adrenal gland measurement is 12.2 mm.

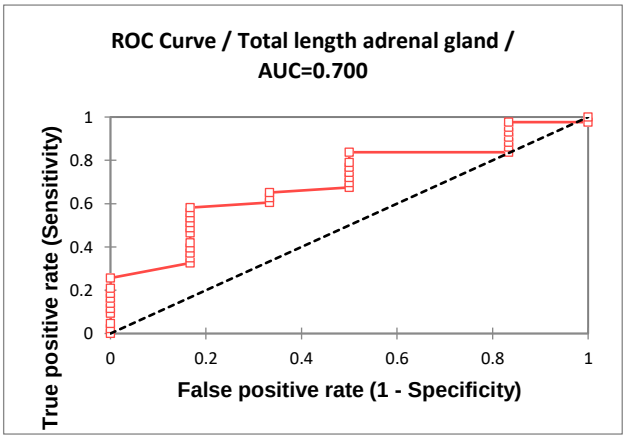

Figure 1 – Analysis of total length of adrenal gland using a ROC curve for predicting delivery within seven days of the measurement. It has not been found any statistical difference for the detection of delivery within 7 days in terms of sensitivity and specificity.

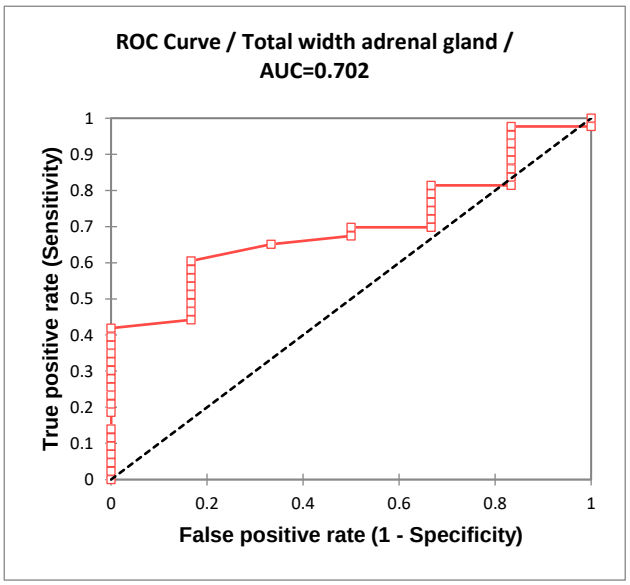

Figure 2 – Analysis of total width of adrenal gland using a ROC curve for predicting delivery within seven days of the measurement

Figure 3 displays results of ROC analysis for the total width of adrenal gland measurement considering an 88% prevalence of delivery within 7 days. The area under the ROC curve is 0.702 (95% confidence interval 0.460–0.943) (p = 0.101). The best obtained cutoff for the total width of adrenal gland measurement is 5.39 mm.

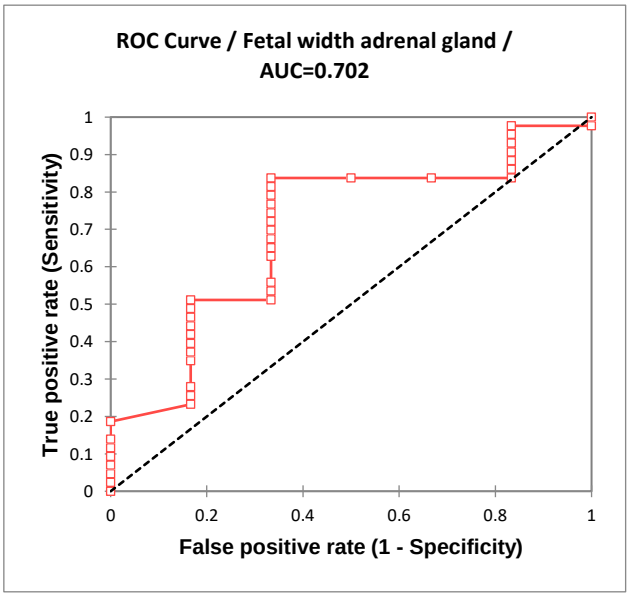

Figure 3 – Analysis of fetal width of adrenal gland using a receiver operating characteristics (ROC) curve for predicting delivery within seven days of the measurement

To reveal the increased performance of the three measurement Figure 4 presents the analysis of the ROC curve for the cervix length considering an 87.8% prevalence of delivery within 7 days.

The ROC curve is 0.640 (95% confidence interval 0.572–0.707) (p < 0.0001). The smaller area under the ROC curve, comparative to the analyses based on adrenal gland measurements, proves that fetal adrenal gland biometry has better predictive values than cervical length.

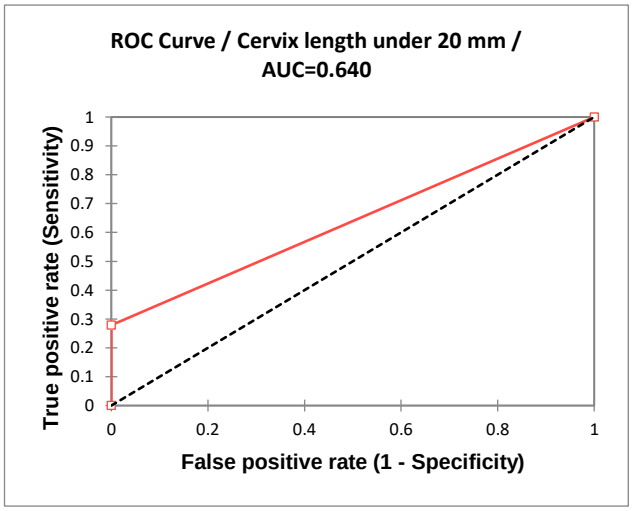

Figure 4 – Analysis of cervix length under 20 mm using a ROC curve for predicting delivery within seven days of the measurement

Table 3 displays the summary statistics of the estimated fetal weight, total length adrenal gland, total width adrenal gland and fetal width. The correlation coefficients displayed in Table 4 reveal a positive correlation between the estimated fetal weight and respectively the total length adrenal gland, the total width adrenal gland and the fetal width adrenal gland.

DISCUSSION

Parturition and labor onset are a complex biological cascade whose origin consist in activation of fetal hypothalamus and pituitary glands in response to fetal stress. Thus, the fetal adrenal gland is activated, and the central area of the gland responds by releasing glucocorticoids, especially DHEA-S. The release of prostaglandins such as PGE2 and PGF2a is the consequence of the interaction of the fetal adrenal gland and the placenta that positively activates CRH, and this leads to onset of labor [17], [18]. Premature activation of placental CRH, acts as a biological clock in early onset of labor and delivery [11]. Therefore, placental activation by fetal steroid precursors may be correlated with fetal adrenal gland enlargement, which was also demonstrated by a previous

autopsy study indicating greater gland weight in preterm neonates [8]. Turan et al. showed that the volume of the adrenal gland was significantly larger in the fetus born prematurely [14]. Another study contradicts these results, showing that the adrenal glands are significantly smaller in spontaneous preterm births [19].

Variable	Observations	Minimum	Maximum	Mean	Std. deviation
Estimated fetal weight	49	697.000	3100.000	1884.061	560.678
Total length adrenal gland	49	15.000	32.000	25.335	3.791
Total width adrenal gland	49	7.140	15.800	12.551	1.920
Fetal width adrenal gland	49	3.700	7.920	6.274	1.029

Table 3 – Summary statistics of the estimated fetal weight, total length adrenal gland, total width adrenal gland and fetal width

In our study we found that the fetal adrenal gland size was higher in women with preterm birth. Are various methods to measure the fetal adrenal gland via transabdominal ultrasound [15], [20], [21]. We choose to focus on two-dimensional total adrenal gland length, total width and fetal zone width. In our study, we assessed 109 right adrenal gland and statistical analysis proves that the symptomatic patients have increased values of the adrenal gland size, without observing any statistically significant differences regarding the total length, total width and fetal zone width.

Variables	Estimated fetal weight	Total width adrenal gland	Total length adrenal gland	Fetal width adrenal gland
Estimated fetal weight	1	0.679	0.663	0.630
Total width adrenal gland	0.679	1	0.979	0.942
Total length adrenal gland	0.663	0.979	1	0.969
Fetal width adrenal gland	0.630	0.942	0.969	1

Table 4 – The correlation matrix

Contrary to our findings, the evaluation of the central fetal adrenal area has been done in some studies, which show in particular the enlargement of the fetal area in cases of premature birth, with a sensitivity of 100% [14].

Hoffman et al. [21] found none of the fetal adrenal gland measures predictive of preterm birth. These conflicting findings are due to the fact that none of the pregnant women delivered within 2 weeks of ultrasound evaluation, and the meantime interval between ultrasound and delivery was 55.3 days. This supports the fact that the fetal adrenal gland undergoes an increase in size in a short interval of time, from 7 to 14 days, and is very predictive in this phase, hypothesis also supported by our study. This concept is consolidated by endocrine research, which has shown that maternal plasma levels of CRH and cortisol are higher in women who deliver within 24 hours [22].

The first data on fetal adrenal gland and preterm birth was offered by Anderson et al. [8] who found higher adrenal glands in autopsies of premature stillbirths. Over time, several studies have been carried out to understand the mechanisms involved in the initiation of delivery by adrenal hormones, but the data related to fetal adrenal gland ultrasound parameters and preterm births are still rare [23], [24].

Turan et al. [25] have remarked that the fetal adrenal gland volume measured both two- and three-dimensional ultrasound could predict delivery within a few days. And when they compared the fetal adrenal gland volume with cervical length measurement, found better predictive values for fetal adrenal gland volume [15]. Our study shows the same results, respectively that fetal adrenal gland biometry is a better predictor of preterm delivery than cervical length.

A study that compared adrenal gland volume (AGV) and fetal zone enlargement (FZE) with cervical length and fetal fibronectin found that AGV and FZE had the highest sensitivity to predict preterm birth within 7 days [26].

Turan et al. [15] have founded that fetal stress as a consequence of preterm birth produces an increase in the central area of the adrenal gland as an adaptive mechanism. Guler et al. [17] analyzed fetal adrenal biometry in women with spontaneous preterm birth and women who gave birth at term. They found that the central zone depth/total fetal adrenal depth ratio was greater in preterm fetuses, but the difference was not statistically significant for the cervical length measurement.

Our research study was motivated by the fact that the identification of markers that help in the development of new strategies for prediction and prevention of preterm delivery and its associated complications is essential.

CONCLUSION

Fetal adrenal glands measurements predicted delivery within 7 days among pregnant women with preterm birth and intact membranes. These results suggest that examination of fetal adrenal gland at the time of evaluating women for symptoms of preterm birth may have major beneficial clinical implications.

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