European Journal of Obstetrics & Gynecology and Reproductive Biology 240 (2019) 341–346

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Fetal adrenal gland size and the ability to predict spontaneous term labor

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ARTICLE INFO

Article history:
Received 5 February 2019
Received in revised form 4 July 2019
Accepted 23 July 2019

Keywords:
Fetal adrenal gland size
Fetal adrenal zone
Spontaneous term labor
Ultrasound measurement
Predicting term labor

ABSTRACT

Objective: The objective of this study was to evaluate whether ultrasound measured fetal adrenal gland size can be a predictor of spontaneous term labor.
Study design: This study was a diagnostic test accuracy study using a prospective cohort design evaluating the ability of 2-dimensional ultrasound measurement of fetal adrenal gland total length, total width, fetal zone length and fetal zone width in women in the third trimester to predict the primary outcome of spontaneous term labor. Secondary outcomes were vaginal delivery, length of labor, and maternal and neonatal morbidities.
Results: Of 43 patients recruited, 3 were excluded. 11 (25.6%) presented in spontaneous labor and 29 (67.4%) underwent induction of labor. Patient demographics were similar for all included except for admission cervical exam and oxytocin use. A receiver operative curve was created to assess test predictability. Weighted width of fetal adrenal gland was the best predictor of spontaneous labor amongst variables measured with an area under the curve of 0.674, $p = 0.93$. $w/W \geq 0.41$ had a sensitivity of 91.0%, specificity of 44.8%, positive predictive value of 38.5% and a negative predictive value of 92.3%. Maternal and neonatal morbidities were not different between the spontaneous labor group and the induction of labor group.
Conclusion: Ultrasound measured fetal w/W was moderately predictive of spontaneous labor.
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Introduction

The process of human parturition is complex, comprised of biochemical, hormonal, and mechanical factors [1]. There is no universal agreement about the series of events that triggers the onset of human labor, although several mechanisms have been postulated. Moreover, the ability to predict the onset of spontaneous term labor is still lacking. Some studies have shown transvaginal ultrasound (TVUS) measurement of cervical length (CL) at term has moderate value in predicting the onset of spontaneous labor, especially with a CL <1–1.5 cm [2,3]. Consequences from false-positive diagnosis of true labor at term are unnecessary hospital admissions, unnecessary obstetrical interventions, increased resource utilization, and increased cost [3].

Fetal adrenal glands have been hypothesized to be the source of the biological signal to start labor in pregnant women [4]. During preterm delivery, abnormal activation of the labor cascade leads to increased dehydroepiandrosterone sulfate (DHEAS) production in the central echogenic area of the fetal adrenal gland, as referred to as the “fetal zone”, with subsequent enlargement of the entire fetal adrenal gland [5,6]. Fetal adrenal size has been used as a quantitative measure of fetal adrenal activity and has been shown to be predictive of spontaneous preterm birth (PTB) [7]. Fetal adrenal size is a quantitative marker easily measured by ultrasound [8]. A study by Turan et al. demonstrated the ability of three-dimensional (3-D) fetal adrenal gland volume (AGV) measurements to predict PTB [9]. When comparing 3-D AGV measurements to a simpler technique using 2-D volume estimation of the fetal adrenal gland, it was found that2-D estimations are not as accurate as3-D calculations for prediction of PTB [10]. However, clinical use of 3-Dimensional fetal AGV measurements is limited by its complexity. On the other hand, it was shown that 2-D measurement of fetal adrenal gland was superior to CL in

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https://doi.org/10.1016/j.ejogrb.2019.07.031
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identifying women at risk for PTB within the next 7 days following the measurement [10]. The objective of this study was to evaluate whether ultrasound measured fetal adrenal gland size could predict spontaneous term labor.

Materials and methods

Study design

This study was a diagnostic test accuracy study using a prospective cohort design evaluating the ability of 2-dimensional ultrasound measurement of fetal adrenal gland total length, total width, fetal zone length and fetal zone width in women in the third trimester to predict the onset of spontaneous term labor [6]. Women who presented to the ultrasound unit for a scheduled biophysical profile at 36–42 weeks of gestational age were asked to participate in the study. After obtaining written informed consent prior to ultrasound, the fetal adrenal gland measurements were collected during the time of their routine scheduled ultrasound. Recruited patients were then followed until spontaneous labor occurred or they underwent an induction of labor. Spontaneous labor was defined as regular, painful contractions every 3–5 minutes that led to cervical change. Data was collected to correlate fetal adrenal gland size with the risk of spontaneous labor onset.

Inclusion criteria were: age 18–50, singleton pregnancy, cephalic presentation, presenting for third trimester ultrasound between 36–42 weeks of gestational age. The authors chose this cohort as these patients as a sample of convenience. Exclusion criteria were: known scheduled cesarean delivery, receipt of 17-alpha hydroxyprogesterone, cerclage, fetal anomalies, planned preterm delivery, known uterine anomaly, multiple pregnancy, intrauterine growth restriction, polyhydramnios, and inability to complete the study.

Women were dated by either first trimester ultrasound consistent with last menstrual period, first trimester ultrasound alone, or second trimester ultrasound consistent with last menstrual period.

The primary outcome of the study was spontaneous term labor and the index was 2-dimensional ultrasound measurements of fetal adrenal gland. The secondary outcome was adrenal gland measures as a predictor of spontaneous vaginal delivery. Maternal morbidities evaluated included 3rd or 4th degree laceration, length of labor, length of second stage of labor, postpartum hemorrhage, transfusion, endometritis and maternal intensive care unit admission. Neonatal morbidities evaluated included neonatal intensive care unit admission, 5 min Apgar score less than 5, chorioamnionitis, any need for continuous positive airway pressure use and neonatal length of stay.

Patient records were reviewed after delivery for these outcomes. This study's IRB approval was provided by Christiana Care Health System.

Ultrasound measurements

Either the left or right fetal adrenal gland [6] was used for measurements using Philips Voluson E8 ultrasound machines and C1-5-D probe 2–5 MHz frequency. Fetal adrenal glands were measured in the same plane. The following measurements were obtained for each participant: length (in mm), width (in mm) of the fetal adrenal gland and the echogenic central fetal zone (Fig. 1a and b). The sonographer repeated each measurement three times with three separate images of the adrenal glands obtained, with the average being used for analysis. Ultrasound measurements were only performed one time during pregnancy. Data was analyzed using the average of the three measurements obtained. A sagittal view of the fetal adrenal gland was preferred to complete the measurements, but a coronal view was also accepted. The final decision of which side and which view of the fetal adrenal gland to use was left up to the certified sonographers. The ratio of total fetal gland width (W) and fetal zone width (w) was used to control for fetal weight. Any participant whose fetal adrenal gland measurements could not be completed was excluded from the study. The obstetricians and patients were blinded to the fetal adrenal gland measurements.

Data analysis

All statistical analysis was performed using SPSS, statistics software for Windows (Version 22.0. IBM Corp., Armonk, NY, USA). Continuous variables were analyzed by t-tests. Categorical variables were analyzed by chi-square test. The ability of the fetal zone width/total fetal adrenal width ratio (w/W), average width, average fetal zone width, weighted fetal zone length (l/L), average length and average fetal zone length were evaluated for prediction of spontaneous labor. Accuracy measures included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A receiver operating characteristic curve was created to assess differing fetal adrenal gland measurements as a test for predicting spontaneous labor.

Results

Of 43 patients recruits, 40 patients met inclusion criteria and completed the study. Three patients were excluded for the following reasons: adrenal gland measurements were unable to be obtained (n = 1), patient underwent a cesarean delivery upon presentation to labor and delivery (n = 2), one for breech presentation, one was elective. Outcomes were available for all included patients and there was no loss to follow up between ultrasound and labor encounters. 11 (27.5%) participants presented in spontaneous labor and 29 (72.5%) underwent an induction of labor. There were no preterm deliveries. The average interval time period of follow up between ultrasound and delivery was 19.5 days (SD 9.1) in the spontaneous labor group vs 10.8 days (SD 10.3) in the induction of labor group ($p = 0.20$). Average gestational age at delivery was 39.8 weeks (SD 1.1) in the spontaneous labor group vs 39.1 weeks (SD 1.1) in the induction of labor group ($p = 0.20$). Patient demographic data between the women who underwent spontaneous labor and the women who underwent induction of labor were similar except for cervical exam at time of admission and oxytocin use, as expected (Table 1).

31 participants had a vaginal delivery (31/40, 77.5%), 6 of which were operative deliveries (6/31, 19.4%, Table 2). Average length of labor in the spontaneous labor group was 14.1 h (SD 5.5) vs. 17.6 h (SD 13.4) in the induction of labor group, ($p = 0.32$, Table 2). Maternal and neonatal morbidities were infrequent (Tables 3 and 4). One participant in each group had a 3rd or 4th degree laceration (9.1% vs. 3.4%, $p = 0.50$). One patient in the induction of labor group required a blood transfusion (0.0% vs. 3.4%, $p = 0.73$). One baby required NICU admission in the spontaneous labor group (9.1% vs. 0.0%, $p = 0.28$). Two deliveries were complicated by chorioamnionitis in the spontaneously labor group compared to one in the induction of labor group (18.2% vs. 3.4%, $p = 0.18$).

A receiver operative curve was created to assess differing fetal adrenal gland measurements as a test for predicting spontaneous labor (Fig. 2). w/W was the best predictor of spontaneous labor amongst variables measured with an area under the curve of 0.67, $p = 0.093$. This was the optimum criterion of the ROC curve to maximize sensitivity and specificity. $w/W \geq 0.41$ had a sensitivity of 91.0%, specificity of 44.8%, PPV of 38.5% and a NPV of 92.3% for

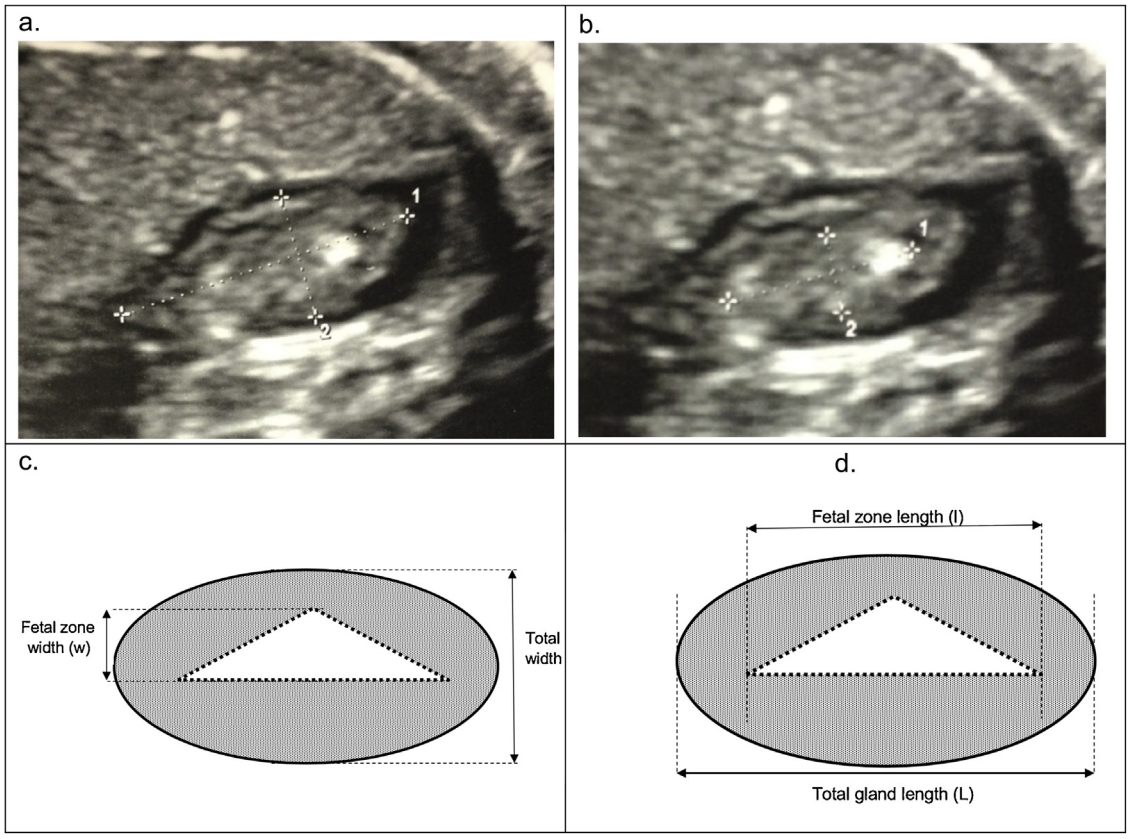

Fig. 1. Ultrasonographic adrenal gland mesaurements.
a) Fetal adrenal – total length x width.
b) Fetal adrenal – fetal zone length x width.
c) Schematic of fetal adrenal gland length measurements.
i. Fetal zone length (l).
ii. Total gland length (L).
d) Schematic of fetal adrenal gland width measurements.
i. Fetal zone width (w).
ii. Total gland width (W).

Table 1
Patient Demographics.

	Spontaneous labor (n = 11)	Induction of labor (n = 29)	P value
Age, years	29.0 (4.9)	30.3 (5.7)	0.5
Gravidity	2.2 (1.1)	1.2 (1.9)	0.1
Parity	0.5 (0.8)	0.8 (1.1)	0.1
Ethnicity			
Hispanic	1.0 (9.1)	2.0 (6.9)	0.6
Non-Hispanic	10.0 (90.9)	27.0 (93.1)	
Race			
Black	5.0 (4.5)	6.0 (20.7)	0.3
White	5.0 (4.5)	17.0 (58.6)	
Asian	1.0 (10.0)	6.0 (20.6)	
Insurance			
Private	9.0 (81.8)	18.0 (62.1)	0.3
Public	2.0 (18.2)	11.0 (37.9)	
BMI at delivery	33.9 (4.0)	34.5 (8.1)	0.7
Diabetes	2.0 (18.2)	7.0 (24.1)	0.5
Hypertension	2.0 (18.2)	10.0 (34.5)	0.3
Gestational age at ultrasound, weeks	37.0 (0.9)	37.5 (1.2)	0.1
Interval between ultrasound and delivery, days	19.5 (9.1)	10.8 (10.3)	0.2
Gestational age at delivery, days	39.8 (1.1)	39.3 (1.1)	0.2

Abbreviations: BMI- body mass index.
Data are in mean ± standard deviation or n (%).

Table 2
Labor Outcomes.

	Spontaneous labor (n = 11)	Induction of labor (n = 29)	P value
Cervical dilation at admission	5.3 (2.6)	2.9 (2.5)	0.02*
Cervical effacement at admission	78.8 (23.8)	60.4 (19.3)	0.04*
Cervical station at admission	0.5 (3.2)	−2.2 (1.9)	0.02*
Epidural	10.0 (90.1)	25.0 (71.4)	0.60
Delivery Type			
Spontaneous vaginal delivery	6.0 (54.4)	19.0 (65.5)	0.05
Operative vaginal delivery	4.0 (36.4)	2.0 (33.3)	
Cesarean delivery	1.0 (9.1)	8.0 (88.9)	
Fetal position			
Occiput anterior	10.0 (90.1)	20.0 (69.0)	0.40
Occiput posterior	0.0 (0.0)	2.0 (6.9)	
Occiput transverse	0.0 (0.0)	2.0 (6.9)	
Unknown	1.0 (10.0)	5.0 (17.2)	
Oxytocin augmentation	5.0 (45.5)	29.0 (100.0)	<0.01*
Artificial rupture of membranes	7.0 (63.6)	22.0 (75.9)	0.35
Male fetus	3.0 (27.3)	18.0 (62.1)	0.05

Data are in mean ± standard deviation or n (%).
* Statistical significance with p value <0.05.

Table 3
Maternal Outcomes.

Maternal Outcomes	Spontaneous labor (n = 11)	Induction of labor (n = 29)	P value
3rd or 4th degree laceration	1.0 (9.1)	1.0 (3.4)	0.5
Labor length, hours	14.1 (5.5)	17.6 (13.4)	0.3
2nd stage length, hours	1.2 (1.8)	1.5 (1.2)	0.6
PPH	0.0 (0.0)	0.0 (0.0)	–
Transfusion	0.0 (0.0)	1.0 (3.4)	0.7
Endometritis	0.0 (0.0)	0.0 (0.0)	–
Maternal ICU admission	0.0 (0.0)	0.0 (0.0)	–

Abbreviations, ICU- intensive care unit, PPH- postpartum hemorrhage.
Data are in mean ± standard deviation or n (%).

Table 4
Neonatal Outcomes.

Neonatal outcomes	Spontaneous labor (n = 11)	Induction of labor (n = 29)	P value
NICU admission	1.0 (9.1)	0.0 (0.0)	0.3
Birth weight	3336.4 (369.6)	3203.3 (436.9)	1.0
5 min Apgar < 5	0.0 (0.0)	0.0 (0.0)	–
Chorioamnionitis	2.0 (18.2)	1.0 (3.4)	0.2
CPAP	0.0 (0.0)	0.0 (0.0)	–
LOS, days	2.6 (1.3)	4.0 (5.4)	0.2

Abbreviations: LOS- length of stay, CPAP- combined positive airway pressure, NICU- neonatal intensive care unit.
Data are in mean ± standard deviation or n (%).

predicting spontaneous labor. w/W was higher in the spontaneous labor group than in the group undergoing an induction of labor, but this was not statistically significant different (p = 0.34, Fig. 3). A receiver operative curve was produced to assess differing fetal adrenal gland measurements as a test for predicting spontaneous vaginal delivery (Fig. 4). None of the curves produced a statistically significant area under the curve (AUC) when using a line of discrimination of 0.5.

Comment

Our study represents a diagnostic test accuracy study using a prospective cohort design demonstrating that ultrasound fetal adrenal gland measurements can be reasonably predictive of spontaneous term labor. Our primary outcome demonstrated that an ultrasound measurement of fetal w/W cut-off point of 0.41 predicted spontaneous term labor with high sensitivity (91.0%) but low specificity (44.8%), making this a good screening test for term spontaneous labor. The negative predictive value of likelihood of going into spontaneous term labor was 92.3% when w/W < 0.41. The PPV of going into spontaneous term labor when w/W > 0.41 was 38.5%. Our secondary outcome found that fetal gland measurements are not predictive of vaginal delivery (Fig. 3).

Consequences from false-positive diagnosis of true labor at term are unnecessary hospital admissions, unnecessary obstetrical interventions, increased resource utilization, and increased cost [3]. False-negative diagnosis of labor at term is less concerning as it can easily be corrected by traditional diagnostics including patient symptoms and progressive cervical dilation on digital vaginal exam. While use of CL on TVUS is widely used to predict PTL, it has limited use for predicting term labor [3]. One small study of 77 patients found that a CL cut off of ≤1-1.5 cm was optimal in predicting true term labor. However, no large study has been done to confirm these findings [3].

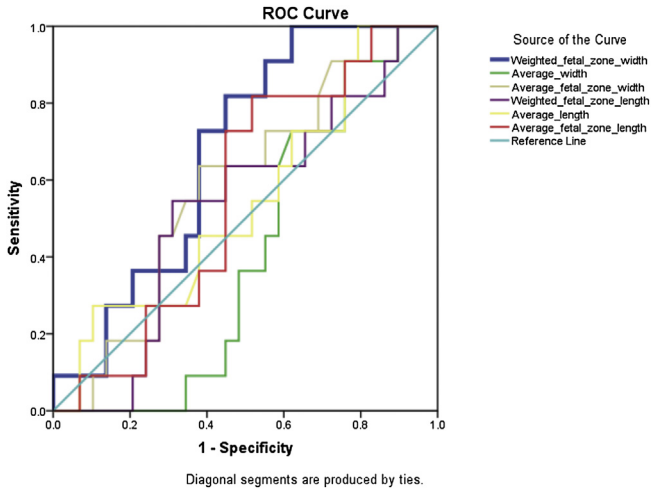

Fig. 2. Spontaneous Labor as Predicted by Fetal Adrenal Measures.
Area Under the Curve:
Weighted fetal zone width (w/W): 0.674, p = 0.093.
Average width: 0.409, p = 0.380.
Average fetal zone width: 0.591, p = 0.380.
Weighted fetal zone length (l/L): 0.530, p = 0.774.
Average length: 0.544, p = 0.672.
Average fetal zone length: 0.561, p = 0.555.
Abbreviations: W- total fetal gland width, w- total fetal zone width, L- total fetal gland length, l-total fetal zone length.

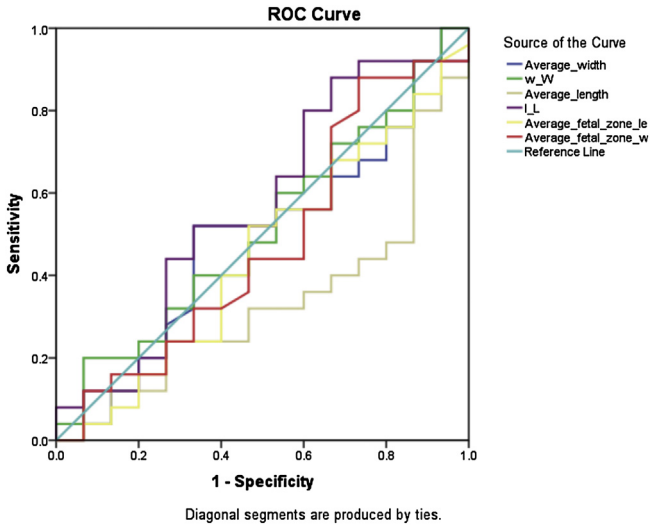

Fig. 4. Spontaneous Vaginal Delivery as Predicted by Fetal Adrenal Measures.
Area Under the Curve:
Average width: 0.489, p = 0.911.
w/W: 0.515, p = .878.
Average length: 0.333, p = 0.081.
l/L: 0.568, p = 0.476.
Average fetal zone length: 0.449, p = 0.596.
Average fetal zone width: 0.476, p = 0.801.

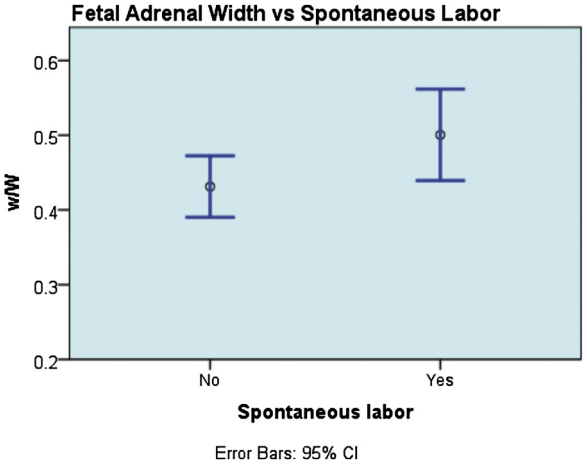

Fig. 3. Fetal Adrenal w/W vs Spontaneous Labor.
p = 0.039.

Our study has several strengths. This was a prospective study that used reliable measurements by trained sonographers, which can be replicated in outpatient clinic and inpatient hospital settings. Moreover, measurements were performed prior to knowing the birth outcomes of patients, successfully blinding the sonographers. Additionally, the obstetricians and patients were blinded to the fetal adrenal gland measurements. No patients were induced based on the measurements obtained in this study. While we did not calculate the estimated fetal weight at the time of the ultrasound fetal adrenal gland measurements, the ratio of total fetal gland width (W) and fetal zone width (w) was used to control for fetal weight. Moreover, there were no differences between groups in birth weight and in the presence of diabetes during pregnancy. Therefore, this is less likely to be a confounder. Most patients who need to undergo an ultrasound in the 3rd trimester have a high likelihood of being scheduled for induction. Therefore, having the ability to predict term labor at this time would reduce the cost of hospital admissions/stays for unnecessary inductions.

There are several limitations to this study. We had a small sample size, meaning a low precision of estimated population parameters. Moreover, our sample population had a large proportion of patients undergoing an induction of labor (n = 29) compared to a spontaneous labor (n = 11). Therefore, our PPV and NPV are not generalizable. There may be a selection bias in our recruited population given that women who need to undergo an ultrasound in the 3rd trimester usually have a medical indication for the exam. Examples include obesity, diabetes, macrosomia, IUGR, hypertension and maternal weight gain. Additionally, some of these medical indications may also be variables that change a woman's labor course, such as a medically indicated induction of labor for diabetes or preeclampsia. This explains why we had a larger proportion of women in the induction of labor group and means that our data may not be as applicable to the general population. We did not record the extra length of time needed by the sonographers to preform adrenal gland measurements, which could be pertinent information to how to apply these measurements clinically. The fetal adrenal gland measurements of length and width were not analyzed separately depending on the coronal or sagittal view of the gland obtained during ultrasound, as the plane used was not reported in our study. This may have led to an overestimation or underestimation of w/W. While this is likely not clinically significant, we could improve our study design by using the same strict fetal gland measurement criteria to every patient. Finally, maternal and neonatal outcomes were too infrequent in this small sample size to conclude differences between groups.

The role of fetal hypothalamic-pituitary-adrenal (HPA) axis was initially established in a sheep model by demonstrating the fact that fetal hypophysectomy causes fetal adrenal atrophy and prevents preterm birth (PTB) [11]. Later, constant maintenance

adrenocorticotropic hormone (ACTH) infusions to increase serum cortisol levels were showed to induce preterm parturition in ovine fetuses [11]. These studies postulate that ACTH plays an essential role in adrenal cortical growth and maturation late in gestation, reflected by increasing basal cortisol concentrations prior to labor onset [11]. In support of this theory, an autopsy study found a significantly increased risk for PTB in fetuses with increased volume of the whole fetal adrenal gland when comparing neonates delivered in the setting of idiopathic PTB to those delivered secondary to fetal/maternal hemorrhage [10]. More recently, fetal adrenal size has been used as a non-invasive quantitative measure of fetal adrenal activity [7]. A disproportionate enlargement of the fetal zone has been shown to reflect an acute premature activation of the parturition machinery and be predictive of spontaneous PTB [7,10]. Measurement of either adrenal gland can provide accurate representation of the fetal zone enlargement in PTB [6]. Therefore, it is reasonable to propose that fetal adrenal measurements of either adrenal gland in this population would also be predictive of spontaneous term labor.

Our study findings showed that ultrasound measured fetal w/W was moderately predictive of spontaneous labor in this small prospective cohort. Further studies are needed with a larger cohort to reduce risk of bias and determine the efficacy and precision of this test in evaluating patients for spontaneous term labor.

Funding disclosure

None.

Declaration of Competing Interest

None declared.

Acknowledgement

None.

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