Original papers

Med Ultrason 2017, Vol. 19, no. 3, 295-301
DOI: 10.11152/mu-981

Can fetal adrenal artery Doppler velocimetry predict delivery date in pregnant women with spontaneous preterm birth?

Francisco Herlânio Costa Carvalho[1], Aline Pinto Lemos[1], Francisco Edson De Lucena Feitosa[1], Helvécio Neves Feitosa[1], Lucas Costa Carvalho Augusto[1], Rosa Maria Salani Mota[1], Edward Araujo Júnior[2]

[1]Fetal Medicine Service, Maternidade-Escola Assis Chateaubriand, Federal University of Ceará (UFC), Fortaleza-CE, [2]Department of Obstetrics, Paulista School of Medicine–Federal University of São Paulo (EPM-UNIFESP), São Paulo-SP, Brazil

Abstract

Aim: To assess the accuracy of delivery date predictions made using fetal adrenal artery Doppler velocimetry in pregnant women with spontaneous preterm birth (PB) and to compare these predictions with cervical length (CL) measurements. **Material and methods:** A prospective study was performed with 51 pregnant women whose gestational lengths were between 24 and 36 weeks. The main outcome was the time between the Doppler velocimetry examination and delivery, categorized as delivery within 7 days or 7 days later after the examination. A receiver operating characteristics curve was performed to define the cutoffs among deliveries within 7 days for fetal adrenal artery Doppler velocimetry parameters and CL measurements. **Results:** The incidence of delivery within 7 days was 37.3%, with a statistically significant difference for the pulsatility index (PI; p=0.045) and resistance index (RI; p=0.030) of the fetal adrenal artery. The best cutoff values of PI and RI for predicting deliveries within 7 days were 1.65 and 0.78, respectively. The sensitivity and specificity of PI, RI, and CL (20 mm) were 73.7% (95% CI: 51.9–95.5) and 56.3% (95% CI: 38.1–74.4); 68.4% (95% CI: 45.4–91.4) and 62.5% (95% CI: 44.8–80.2); and 76.5% (95% CI: 54.0–99.0) and 78.1% (95%: CI 71.1–97.7), respectively. **Conclusion:** Fetal adrenal artery Doppler velocimetry can predict delivery within 7 days among pregnant women in cases of spontaneous PB and this prediction is similar to the predictions made using CL measurements.

Keywords: ultrasonography; preterm birth; fetal adrenal gland; cervical length; Doppler.

Introduction

Health care practitioners have had limited ability to identify pregnant women likely to experience preterm birth. The main preventive interventions for preterm birth, such as vaginal progesterone, are restricted to high-risk pregnancies including women with previous preterm births or those who have a short uterine cervix. However, the majority of preterm births occur in low-risk pregnancies, and all available methods should be used to identify these cases [1].

The identification of several biochemical and biophysical markers has been proposed as a means to identify pregnancies at high risk for spontaneous preterm birth because most high-risk cases are asymptomatic [2]. At present, cervical length (CL) measurement is an excellent ultrasound marker for predicting preterm birth in both high- and low-risk pregnancies [2-4].

In 2007, the first literature description regarding the relevance of fetal adrenal gland volume for predicting preterm births was published. An increase in fetal adrenal gland volume was found to have an accuracy of 98% when used to predict delivery within 5 days [5]. Turan et al [6] demonstrated that fetal adrenal gland volume was a better predictor of preterm birth than CL measurement. In that study, in addition to the increase in total fetal adrenal gland volume, the central zone showed a disproportional increase.

Received 10.10.2016 Accepted 04.01.2017
Med Ultrason
2017, Vol. 19, No 3, 295-301
Corresponding author: Prof. Edward ARAUJO JÚNIOR, Ph.D
Department of Obstetrics, Paulista School of Medicine–Federal University of São Paulo (EPM-UNIFESP)
Rua Belchior de Azevedo, 156 apto. 111
Torre Vitoria, São Paulo–SP, Brazil
CEP 05089-030
Phone/Fax: +55-11-37965944
E-mail: araujojred@terra.com.br

To the best of our knowledge, no studies in literature have examined the use of fetal adrenal artery Doppler velocimetry for the prediction of preterm birth. Therefore, the objective this study was to assess the capacity of fetal adrenal artery Doppler velocimetry to predict delivery within 7 days for pregnant women with intact membranes in cases of spontaneous preterm birth and to compare these predictions with CL measurements.

Materials and methods

The prospective study was conducted between April 2014 and March 2015. Approval by the Local Ethics Committee (nº 640.692) was obtained and the pregnant women provided their informed consent. Singleton pregnant women who were admitted to the hospital with signs or symptoms of spontaneous preterm birth and with gestations between 26 weeks and 34 weeks were invited to participate in the study. Gestational age was determined by the last menstrual period and confirmed by an ultrasound examination performed until the 20th week of pregnancy.

The following signs and symptoms were considered to diagnose spontaneous preterm birth: abdominal pain with uterine contractions, modifications of the uterine cervix, and the need for tocolytic medication. The assessment of uterine contractions was routinely performed during a 20 minute period but we took into consideration any number of regular uterine contractions that were capable to produce cervical changes and necessitate tocolytic medication for inclusion in this study. Cervical changes were assessed by vaginal examination at 1–2 hour intervals. All pregnant women with risk of impeding spontaneous preterm birth, except for pregnant women who were at least 34 weeks of gestation, received oral nifedipine (20 mg) as tocolytic medication for at least 24 h and intramuscular dexamethasone for fetal lung maturation (12 mg, two doses, 24 h intervals). If contractions persisted after 30 min, a second dose of nifedipine (20 mg) was administered orally followed by another 20 mg every 8 h for 48 h. The exclusion criteria were as follows: premature rupture of membranes, pregestational and gestational diabetes mellitus, chronic arterial hypertension, pre-eclampsia, endocrine diseases, amniotic fluid disorders (amniotic fluid index <5 cm or >25 cm), fetal malformations detected during the ultrasound examination and/or confirmed in the postnatal exam, fetal distress detected by cardiotocography, suspicion of fetal growth restriction (estimated fetal weight <10th percentile for gestational age [7] and/or umbilical artery pulsatility index >95th percentile or cerebroplacental ratio <5th percentile at Doppler velocimetry [8]), maternal use of vaginal progesterone to prevent spontaneous preterm birth or spontaneous preterm birth treatment during the actual pregnancy, and newborn size that was too small or too large for gestational age according to the Alexander curve [9]. It was a study protocol unpublished in the literature and because of lack of all the changes that may occur in the fetal adrenal gland with growth impairment (large or small for gestational age), we decided to select a very homogeneous population.

The ultrasound exams were performed within 24 h of hospital admission using a Voluson S6 apparatus (General Electric Medical Systems, Milwaukee, WI, USA) equipped with a convex probe (4C-RS). The sonographic evaluation of the CL measurement was performed transvaginally. Fetal adrenal artery Doppler velocimetry assessment was performed according to the procedure described by Fujita et al [10] using the transabdominal route. With the mothers in the semi-Fowler position, an axial view of the fetal abdomen was obtained at the level of the adrenal glands. Color and/or power Doppler velocimetry were applied to identify the middle adrenal artery, which is an aortic branch, at the level of the adrenal gland hilum. To the posterior side, the gate of the spectral Doppler velocimetry was positioned closest to the midpoint of the fetal adrenal artery in the absence of uterine contractions or respiratory or body movements of the fetus. The following Doppler velocimetry settings were standard in all exams: filter 100 Hz, sample size 2 mm, and insonation angle ≤30°. When at least three typical waveforms were obtained, the pulsatility index (PI), resistance index (RI), and systole/diastole (S/D) ratio were measured by ultrasound apparatus automatically in one waveform. We also assessed the presence or absence of end-diastolic flow (fig 1).

All ultrasound exams were performed by a single certified examiner (FHCC) with 15 years of experience in obstetrical ultrasound. This examiner performed a learning curve with 20 adrenal artery Doppler velocimetry exams prior to the study to increase the intra-observer reproducibility of measurements.

Pregnant women were followed through by using the institutional protocol with 100 mcg/day vaginal progesterone if there was cessation of uterine contractions. In all deliveries that occurred before 32 weeks, the pregnant women received magnesium sulfate to protect the fetal brain during the active phase of delivery or 2 h before elective cesarean section [magnesium sulfate 6 g bolus IV over 20–30 min and maintenance with 2 g/h (in 5% dextrose using a pump)]. Magnesium sulfate was discontinued if delivery did not occur after 12 h, if the delivery was no longer considered imminent or after 24 h from the initial dose [11]. When deliveries occurred in

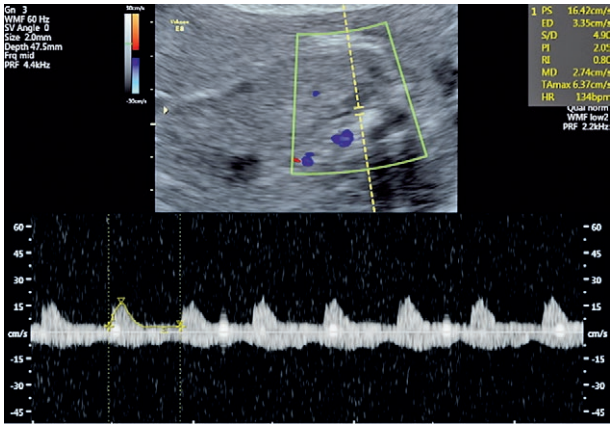

Fig 1. Color Doppler velocimetry were applied to identify the mean adrenal artery, which is an aortic branch, at the level of the adrenal gland hilum. To the posterior side, the gate of the spectral Doppler velocimetry was positioned in the fetal mean adrenal artery closest to the probe. When at least three typical waveforms had been obtained, the PI, RI, and S/D ratio were measured automatically in one waveform. PI: pulsatility index, RI: resistance index; S/D ratio: systole/diastole ratio.

the *Maternidade-Escola Assis Chateaubriand* – Federal University of Ceará, the data were obtained by medical records. When the birth did not occur in the institution, the data were obtained by phone calls with the patients.

The following variables were measured: maternal data (age, parity, history of prior preterm birth, gestational age at ultrasound examination); Doppler examination data (PI, RI, S/D ratio, and presence or absence of end-diastolic flow), perinatal outcome data (time between the Doppler velocimetry examination and delivery, gestational age at delivery, delivery route, birth weight and Apgar score at 1st and 5th minute).

The outcome variable was the time period between the Doppler velocimetry examination and delivery, which was classified into two groups: delivery within 7 days and delivery after 7 days. We chose dichotomizing similarly to Turan et al [6].

Statistical analysis

The sample size was calculated considering the high prevalence of suspected diagnosis of preterm birth at Maternidade-Escola Assis Chateaubriand – Federal University of Ceará and to differentiate true from false preterm birth by ultrasound and fetal adrenal artery Doppler velocimetry, since we did not use fibronectin or other biochemical markers to evaluate patients with suspicion of preterm birth. We decided to calculate the sample size considering the risk of delivery within 7 days in symptomatic pregnant women (36.5%) [6], a significance level of 5% (alpha error 0.05 - two-sided), 90% power (beta error of 10%), and bias of 20% (alternative p=0.175). A minimum of 52 subjects would be necessary for this study.

Data were transferred to an Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed using the PASW Statistics program (version 20.0; SPSS Inc., Chicago, IL, USA). Fisher's exact test to nominal variables was applied, and either the Mann–Whitney U test or Student *t*-test to continuous variables. A receiver operating characteristics (ROC) curve was performed to predict the best cutoffs regarding delivery within 7 days to fetal adrenal Doppler velocimetry artery and CL measurement. A point on the ROC curve near the top left corner was selected, with smaller proportions of false positives and false negatives. We prioritized getting better specificity rather than sensitivity because the aim was not a screening test, but to obtain a test to support the diagnosis of true preterm labor applicable in clinical practice. Sensitivity, specificity, positive predictive value, false positive, negative predictive value, false negative, positive likelihood ratio, and negative likelihood ratio were calculated. McNemar's test was applied to compare the sensitivity and specificity regarding delivery within 7 days between the obtained cutoffs for adrenal artery PI and RI values, and CL measurement (20 mm). The relative risk of these cutoffs to delivery within 7 days as well as the prediction capacity for variables combination were calculated, which turned out to be good predictors (both below the cutoff points) of delivery occurring within 7 days. A P value of less 0.05 was considered an indicative of statistical significance.

Results

We initially selected 64 pregnant women but 13 were excluded for the following reasons: one fetus had hydronephrosis, one newborn was small for gestational age, one pregnant woman had pre-gestational diabetes mellitus, one pregnant woman had gestational diabetes, two pregnant women had chronic arterial hypertension, Doppler velocimetry of the adrenal artery was not assessed in two cases due to technical difficulties (one case of maternal obesity and one case of excessive fetal movement), and five pregnant women missed the follow-up.

Therefore, data from 51 pregnant women were used for the statistical analysis. A total of 19 (37.3%) mothers had their deliveries within 7 days from hospital admission.

Table I shows the maternal characteristics and perinatal outcomes for both groups. The assessment of fetal mean adrenal artery Doppler velocimetry was possible for 51 out of 56 patients (51 regularly included patients and 5 missing follow-ups) with a 91.1% success rate.

Table II shows the comparison of Doppler velocimetry parameters between both groups.

The ROC curve for the mean fetal adrenal artery PI for a 37.3% prevalence of delivery within 7 days had an area under the ROC curve of 0.669 (95% CI: 0.523–0.816, p=0.045) with an optimal selected cutoff of 1.65. The ROC curve for the mean RI of the fetal mean adrenal artery had an area under the ROC curve of 0.679 (95% CI: 0.528–0.831, p=0.034), with an optimal selected cut-off of 0.78. Table III shows the sensitivity, specificity, positive predictive value, false positive, negative predictive value, false negative, positive likelihood ratio, and negative likelihood ratio for PI (cutoff 1.65), RI (cutoff at 0.78), and CL measurement (cutoff at 20 mm).

The area under the ROC curve for CL measurement was 0.807 (95% CI: 0.663-0.951, p<0.001) and the S/D ratio of the fetal adrenal artery was 0.548 (95% CI 0.411-0.692, p=0.39). The relative risk of delivery to occur over the next 7 days for CL measurement <20 mm was 5.6 (95% CI: 2.2-14.6), RI <1.65 was 2.3 (95% CI: 1.0-5.4), and PI <0.78 was 2.3 95% CI: 1.0-4.9).

There were no significant differences in sensitivity or specificity for the detection of delivery within 7 days, using the MacNemar test. Sensitivity of the mean

Table I. Distribution of maternal and perinatal characteristics according to the outcome.

Characteristics	**All cases (n = 51)**	**Delivery ≤7 days (n = 19)**	**Delivery >7 days (n = 32)**	**p**
Maternal age	23.4±6.4	25.2±7.8	23.9±5.9	0.37#
Parity	0.8±0.7	0.9±0.6	0.8±0.8	0.96#
Race				
Non white	21 (41.2)	9 (42.9)	12 (57.1)	0.79*
White	30 (58.8)	10 (33.3)	20 (66.7)	
GA (weeks)	31.9±3.6	32.2±3.7	31.6±3.6	0.46#
Previous prematurity				
No	42 (82.4)	14 (33.3)	27 (66.7)	0.73*
Yes	9 (17.6)	4 (44.4)	5 (55.6)	
Corticoid				
Yes	48 (94.1)	19 (35.7)	31 (64.6)	0.61*
No	3 (5.9)	4 (66.7)	1 (33.3)	
US performed after corticoid administration				
Yes	45 (84.9)	15 (78.9)	28 (87.5)	0.83*
No	8 (15.7)	4 (21.1)	4 (12.5)	
Perinatal outcome:				
GA at delivery (weeks)	35.8±3.8	34.1±3.7	37.4±3.5	0.032&
Birth weight (g)	2519.3±661.2	2033.6±658.1	2936.4±492.3	< 0.001&
Type of delivery				
Cesarean section	19 (37.3)	8 (42.1)	11 (57.9)	0.78*
Vaginal	32 (62.7)	11 (34.4)	21 (65.9)	
Sex of newborn				
Male	29 (56.9)	11 (37.9)	18 (62.1)	1.00*
Female	22 (43.1)	8 (36.4)	14 (63.6)	

The results are expressed as n(%) or mean± standard deviation, US: ultrasound, GA: gestational age, *Fisher's exact test, #Student's t test, &Mann–Whitney U test

Table II. Distribution of fetal adrenal artery Doppler parameters according to the outcome.

Doppler parameter	**All cases**	**Delivery ≤7 days**	**Delivery >7 days**	**p**
End-diastolic peak				
Positive	34 (66.7)	16 (47.1)	18 (52.9)	0.07*
Absent	17 (33.3)	3 (17.6)	14 (82.4)	
RI	0.80±0.17	0.74±0.15	0.84±0.17	0.030&
PI	1.71±0.85	1.36±0.35	1.91±0.99	0.045&
Systole/diastole ratio	5.30±7.85	4.04±2.20	6.30±4.46	0.56&

The results are expressed as n(%) or mean± standard deviation, RI: resistance index, PI: pulsatility index, *Fisher's exact test, &Mann–Whitney U test

Table III. Comparative analysis between the different cutoffs of fetal adrenal artery Doppler parameters and cervical length measurement.

Variable	Se (95% CI)	Sp (95% CI)	PPV	NPV	Accuracy	LR+	LR−
Positive end-diastolic peak	61.1% (41.2-82.3)	73.5% (55.3-94.9)	56.3%	77.2%	69.1%	2.309	0.529
PI ≤1.65	73.7% (51.9-95.5)	56.3% (38.1-74.4)	48.4%	79.3%	62.5%	1.684	0.468
RI ≤0.78	68.4% (45.4-91.4)	62.5% (44.8-80.2)	50.4%	78.0%	64.6%	1.825	0.505
Cervical length <20 mm	76.5% (54-99)	78.1% (71.1-97.7)	66.1%	85.6%	77.5%	3.493	0.301

95% CI: 95% confidence interval; PI: pulsatility index; RI: resistance index; Se: sensitivity; Sp: specificity; PPV: positive predictive value; FP: false positive; NPV: negative predictive value; FN: false negative; LR+: positive likelihood ratio; LR−: negative likelihood ratio.

adrenal artery PI (73.7%) versus the CL (76.5%) measurement was p=1.00 and versus the mean adrenal artery RI (68.4%) was p=1.000. The specificity of the mean adrenal artery PI (73.5%) compared to the CL (78.1%) measurement was p=0.21 and that compared to the mean adrenal artery RI (62.5%) provided a value of p=1.00.

The ability of delivery prediction occurrence within 7 days by the combination of variables below the cutoffs was calculated. For the combination of cervical biometry with RI (both below the cutoff points), sensitivity was 94.4% (95% CI: 82.7-100.0), specificity was 48.4% (95% CI: 29.8–67.0), accuracy was 31.1%, positive likelihood ratio was 1.83, and negative likelihood ratio was 0.12. For the combination of cervical biometry with PI (both below the cutoff points), the sensitivity was 88.9% (95% CI: 72.8–100.0), specificity was 45.2% (95% CI: 26.6–63.7), accuracy was 29.0%, positive likelihood ratio was 1.62, and negative likelihood ratio was 0.25.

Discussions

This study is the first one, to the best of our knowledge, to test the hypothesis that the fetal adrenal artery reduces its resistance in cases of imminent preterm birth. We observed that both PI and RI were good predictors of delivery within 7 days for pregnant women in cases of spontaneous preterm birth, suggesting that Doppler velocimetry indices could be incorporated into the obstetrics practice together with biophysical (CL measurement [2,4] and fetal adrenal biometry [5,6]) and biochemical markers [12] to obtain a greater predictive power for preterm birth in symptomatic pregnant women.

Previous observations have shown vasodilation in the adrenal artery of fetuses with chronic hypoxemia [13-15]. These studies describe the presence of vasodilatation in the fetal adrenal artery as being associated with prematurity, higher Cesarean section rates, fetal distress detected by cardiotocography, and longer time periods spent in neonatal intensive care units.

The only reference range of the fetal mean adrenal artery PI was described by Mari et al [15]. They assessed 131 singleton pregnancies and observed that PI values decreased with increasing gestational age. The authors did not observe statistically significant differences between the PI of the mean adrenal artery and the PI of the inferior adrenal artery or between the right or left adrenal arteries. The success rate of obtaining the Doppler velocimetry waveforms was 84% and the intra-observer reproducibility was 7.4%. Dudiel et al. [13] had a success rate of 81% for obtaining the Doppler waveform parameters, with failures due to fetal movements. In our study, we obtained a 96% success rate, which could be hypothesized as a consequence of using a higher-quality ultrasound apparatus today.

Fujita et al [10] described a success rate of 90% in obtaining Doppler velocimetry waveforms in the fetal mean adrenal artery and 50% in the fetal superior adrenal artery. The fetal inferior adrenal artery was not identified in 10 attempts. These authors stated that RI values increased until the 31st week of gestation and progressively decreased after this age. Fetal adrenal artery Doppler velocimetry showed the ability to differentiate among fetuses with high risks for hypoxemia and those with adverse perinatal outcomes [14,15].

It has been shown that the volume of the fetal adrenal gland enlarges in the last 6 weeks before term or preterm delivery, especially with disproportionate increase between the central and the peripheral areas 5 to 7 days before preterm birth. Fetal adrenal gland synthesizes steroid precursors which are transformed into estrogen by the placenta. It has been suggested that this increase of fetal adrenal gland, particularly its central zone may have an important role in the endocrine regulation of parturition. [6,16-18]. Turan et al [6] considered reasonable to propose that a disproportionate increase in the size of the

fetal adrenal gland would allow noninvasive recognition of premature activation of the delivery cascade.

Therefore, higher vascularization would be necessary to increase the volume of this gland. The formulated hypothesis was based on the fact that there was an increase of the gland in consequence of the increased vascularity. In other words, the reduced resistance in the fetal adrenal artery Doppler velocimetry should reflect the increase in the vascularization concomitant with the increase in the volume.

According to Ishimoto et al [17], the central zone of the fetal adrenal gland produces large amounts of androgens, which are transformed into estrogens in the placenta. Therefore, the human fetus presents with large adrenal glands, and after delivery, these glands involute quickly, decreasing by 50%, because of decreased androgen secretion. The growth of the fetal adrenal gland involves proliferation, hypertrophy, apoptosis, and cellular migration [9]. The biometry of the central zone, because of its disproportionate increase relative to the total gland, has been found to be a good predictor of imminent preterm delivery in pregnant women [6]. A specific study on the vascularization of the central zone could perhaps contribute to a better understanding of the function of the fetal adrenal gland in determining delivery.

In our study, all of the pregnant women had intact membranes. Turan et al [5,6,19] assessed fetal adrenal gland volume in a heterogeneous population of pregnant women, including 34% with premature rupture of membranes [5]. The mechanisms involved in preterm birth in the presence of premature membrane rupture are associated with inflammatory and infectious factors, and it is not known what effect these factors could have on the volume and vascularization of the fetal adrenal gland [20]. Moreover, scientific evidence shows that antibiotic prophylaxis increases the latency period in pregnant women with premature rupturing of the membranes [21].

In our protocol, we recorded whether steroids administration occurred before or after the fetal adrenal artery Doppler assessment. There were no statistically significant differences between the groups suggesting similar corticoid effects on delivery in both groups.

Statistical analysis to associate the risk of delivery within 7 days in this population were performed using the same data used to define the cutoff points (values of PI and RI for predicting delivery within 7 days were 1.65 and 0.78, respectively). Therefore, these estimates may be biased and should be considered as a study limitation. These cutoff points should be tested in other populations and institutions.

Considering the need for specific operator training and time for scanning as well as cost and considering that at the end the predictive value of fetal adrenal artery Doppler velocimetry is similar to CL measurement, it becomes apparent that the clinical usefulness of this method in order to be proposed or included in obstetrical practice is very limited if not recommendable.

Conclusions

In conclusion, fetal adrenal artery Doppler velocimetry was identified as a good predictor of delivery in pregnant women who had spontaneous preterm births with intact membranes. The predictive value of this method was similar to that of CL measurements. However, future studies with larger population size are warranted to demonstrate the real significance of fetal adrenal artery Doppler velocimetry in predicting preterm births.

Conflict of interest: none

References

1. Tedesco RP, Passini R, Cecatti JG, Camargo RS, Pacagnella RC, Sousa MH. Estimation of preterm birth rate, associated factors and maternal morbidity from a Demographic and Health Survey in Brazil. Mater Child Health J 2013;17:1638-1647.
2. Di Renzo GC, Roura LC, Facchinetti F, et al. Guidelines for the management of spontaneous preterm labor: identification of spontaneous preterm labor, diagnosis of preterm premature rupture of membranes, and preventive tools for preterm birth. J Mater Fetal Neonatal Med 2011;24:659-667.
3. Orzechowski KM, Boelig R, Nicholas SS, Baxter J, Berghella V. Is universal cervical length screening indicated in women with prior term birth? Am J Obstet Gynecol 2015;212:234.e1-5.
4. Lim K, Butt K, Crane JM. SOGC Clinical Practice Guideline. Ultrasonographic cervical length assessment in predicting preterm birth in singleton pregnancies. J Obstet Gynaecol Can 2011;33:486-499.
5. Turan OM, Turan S, Fuani EF, Buhimschi IA, Copel JA, Buhimschi CS. Fetal adrenal gland volume. A novel method for identify women at risk for impending preterm birth. Obstet Gynecol 2007;109:855-862.
6. Turan OM, Turan S, Funai EF, et al. Ultrasound measurement of fetal adrenal gland enlargement: an accurate predictor of preterm birth. Am J Obstet Gynecol 2011;204:311e1-10.
7. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology 1991;181:129-133.
8. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther 2014;36:86-98.

9. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163-168.
10. Fujita Y, Satoh S, Nakano H. Doppler velocimetry in the adrenal artery in human fetuses. Early Human Dev 2001;65:47-55.
11. Rouse DJ, Hirtz DG, Thom EA, et al. A randomized trial of magnesium sulfate for the prevention of cerebral palsy. New Engl J Med 2008;359:895-905.
12. Chauhan SP, Berghella V, Sanderson M, Magann EF, Morrison JC. American College of Obstetricians and Gynecologists practice bulletins: an overview. Am J Obstet Gynecol 2006;194:1564-1572.
13. Dubiel M, Breborowicz GH, Marsal K, Gudmundsson S. Fetal adrenal and middle cerebral artery Doppler velocimetry velocimetry in high-risk pregnancy. Ultrasound Obstet Gynecol 2000;16:414-418.
14. Mari G, Uerpairojkit B, Abuhamad AZ, Copel JA. Adrenal artery velocity waveforms in the appropriate and small-for-gestational-age fetus. Ultrasound Obstet Gynecol 1996;8:82-86.
15. Mari G, Abuhamad AZ, Uerpairojkit, B, Martinez E, Copel JA. Blood flow velocity waveforms of the abdominal arteries in appropriate-and small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 1995;6:15-18.
16. Guler A, Pehlivan H, Cakmak B. Assessment of fetal adrenal gland enlargement in term and preterm labor cases. Int J Res Med Sci 2015;3:1035-1040.
17. Ishimoto H, Jaffe RB. Development and function of the human fetal adrenal cortex: a key component in the feto-placental unit. Endocr Rev 2011;32:317-355.
18. Challis JR, Bloomfield FH, Bocking AD, et al. Fetal signals and parturition. J Obstet Gynaecol Res 2005;31:492-499.
19. Turan OM, Turan S, Buhimschi IA, et al. Comparative analysis of 2-D versus 3-D ultrasound estimation of the fetal adrenal gland volume and prediction of preterm birth. Am J Perinatol 2012;29:673-680.
20. ACOG. Practice bulletins No. 139: premature rupture of membranes. Obstet Gynecol 2013;122:918-930.
21. Menon R, Fortunato SJ. Infection and the role of inflammation in preterm premature rupture of the membranes. Best Pract Res Clin Obstet Gynaecol 2007;21:467-478.