Original Research

Antenatal Testing for Women With Preexisting Medical Conditions Using Only the Ultrasonographic Portion of the Biophysical Profile

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OBJECTIVE: To report the utility of the ultrasonographic biophysical profile, which includes all the components of a biophysical profile minus the nonstress test, in women with maternal indications for antepartum surveillance.

METHODS: We conducted a case series reviewing the records of all women at 32 weeks of gestation or greater with at least one indication for antenatal testing (per the American College of Obstetricians and Gynecologists) delivered by a single maternal–fetal medicine practice between 2006 and 2018. Indications included diabetes, hypertension, lupus, antiphospholipid syndrome, sickle cell disease, renal disease, heart disease, hyperthyroidism, isoimmunization, inherited thrombophilia, and prior intrauterine fetal demise. Weekly ultrasonographic biophysical profiles were initiated at 32 weeks of gestation. We calculated the test-positive rate, the percentage of women delivered for an abnormal ultrasonography biophysical profile, and the intrauterine fetal demise rate (false-negative rate).

RESULTS: Nine hundred eighty-five women underwent 3,981 ultrasonographic biophysical profiles (four per woman; range 1–11). Sixteen women had an abnormal ultrasonographic biophysical profile, for a test positive rate of 1.6% (95% CI 1.0–2.6%) per woman, or 0.4% (95% CI 0.3–0.7%) per ultrasonographic biophysical profile. Of the 16 women with abnormal ultrasonographic biophysical profiles, 13 were delivered with good outcomes and three women had normal follow-up testing and uncomplicated deliveries at a later date. There were three women with intrauterine fetal demise (false-negative rate of 0.3%, 95% CI 0.1–0.9%). One woman with intrauterine fetal demise had a factor V Leiden mutation, fetal ventriculomegaly, and fetal growth restriction. The second woman with intrauterine fetal demise had advanced maternal age, a factor V Leiden mutation, and fetal growth restriction. The third woman with intrauterine fetal demise had class B diabetes. All three intrauterine fetal demises were diagnosed antepartum with an interval from normal ultrasonographic biophysical profile to intrauterine fetal demise of 7, 7, and 6 days, respectively.

CONCLUSION: The use of ultrasonographic biophysical profile in a high-risk cohort is associated with a very low test-positive rate and a very low incidence of intrauterine fetal demise. In women with preexisting medical conditions that place them at higher risk for intrauterine fetal demise, ultrasonographic biophysical profile can be used for antenatal testing.

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In the United States, the rates of chronic disease among pregnant women have increased over the past two decades; today almost 10% of women giving birth have at least one preexisting medical condition.[1] These conditions place women at increased risk for adverse neonatal outcomes, including intrauterine fetal death.[2] For these women, antenatal fetal testing

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is used to identify fetuses at risk for intrauterine fetal death and neurologic complications from intrauterine hypoxia. Identifying these at-risk fetuses is important, because obstetricians can potentially intervene at the appropriate time to prevent adverse outcomes. The American College of Obstetricians and Gynecologists (ACOG) has identified maternal indications for antenatal testing that place women at higher risk for fetal demise.[3] These include chronic conditions such as diabetes, hypertensive disorders, and antiphospholipid syndrome as well as poor obstetric history such as prior intrauterine fetal death. Despite the widespread integration of antepartum surveillance into clinical practice, there remains a paucity of evidence from randomized controlled trials about the efficacy of this testing.[4]

There are several different techniques that are used for antepartum surveillance. These modalities rely on the fact that fetal behavioral activities are regulated by discrete centers in the fetal brain that are sensitive to local factors and peripheral sensors.[4] Hypoxemia and acidemia are thought to result in neuronal suppression of these activities. However, other factors such as fetal sleep states may affect these fetal parameters. The most commonly used method is the nonstress test; a reactive test is predictive of an uncomplicated perinatal outcome, and a nonreactive test is associated with perinatal morbidity and mortality.[5] This test is associated with a significant false-positive rate, cited to be as high as 55–90%.[6,7]

Biophysical profiles have been shown to be a more sensitive and specific marker for fetal well-being than the nonstress test.[6] A traditional biophysical profile assesses fetal breathing, fetal movement, fetal tone, amniotic fluid volume, and includes the nonstress test component. The scoring method used for each parameter is binary; a normal parameter is assigned a score of 2 and an abnormal parameter is assigned a score of 0. These parameters provide an indication of fetal neurologic integrity and are sensitive to acute and chronic changes in oxygen status. In our practice, we have been using the ultrasonographic portion of the biophysical profile (ultrasonographic biophysical profile, ie, all components except for the nonstress test) as the primary modality for fetal assessment with reflex nonstress test evaluation in the setting of any abnormal parameter of the biophysical profile evaluation. Previous studies have shown a low false-positive rate defined as an abnormal ultrasonographic biophysical profile that did not diagnose a intrauterine fetal death or lead to an iatrogenic delivery (1.9%, 95% CI 1.0–3.4%) and low incidence of intrauterine fetal death (0.4%, 95% CI 0.1–1.3%) when ultrasonographic biophysical profile was used for antenatal surveillance in twin pregnancies.[5] Similarly, the use of the ultrasonographic biophysical profile was associated with a low risk for intrauterine fetal death at 36 weeks of gestation or greater (0.14%) for women with advance maternal age.[8] Few other studies have examined the utility of ultrasonographic biophysical profile in high-risk singleton gestations during antepartum surveillance.

In this study, we sought to report the utility an ultrasonographic biophysical profile in singleton pregnancies with maternal indications for antepartum surveillance.

MATERIALS AND METHODS

We conducted a case series reviewing the records of all women delivered by a single maternal–fetal medicine practice unit from January 2006 to March 2018 with singleton pregnancies at 32 weeks of gestation or greater and a maternal indication for antenatal testing. We excluded pregnancies with fetal aneuploidy or major congenital anomalies discovered before or after birth. For this study, we included only women with indications for antenatal testing that are generally accepted and listed by ACOG[3]: pregestational diabetes, gestational diabetes requiring medication, chronic or gestational hypertension and preeclampsia, systemic lupus erythematosus, antiphospholipid antibody syndrome, sickle cell disease, chronic renal disease, congenital heart disease, hyperthyroidism, isoimmunization, and prior intrauterine fetal death (20 weeks of gestation or greater). Over the course of the study period we also performed ultrasonographic biophysical profiles starting at 32 weeks of gestation or greater for women with inherited thrombophilias (factor V Leiden mutation, prothrombin gene mutation, protein C or S deficiency, antithrombin deficiency) because these patients typically underwent inherited thrombophilia testing (by us or before being referred to us) only for poor obstetric histories. Because this indication is not listed by ACOG,[3] we analyzed our data including and excluding patients with this indication for antenatal testing. We did not include women undergoing antenatal testing solely for fetal indications (such as fetal growth restriction), but women with a maternal indication for testing who developed fetal growth restriction were included.

In our practice, the ultrasonographic biophysical profile is initiated at approximately 32 weeks of gestation. Ultrasonographic biophysical profiles are performed weekly and do not routinely include Doppler assessment of fetal or umbilical cord vessels. The patients also undergo growth ultrasonograms

every 4 weeks. More frequent testing or initiation of Doppler assessment is performed only if clinically indicated, such as in the setting of fetal growth restriction.

Our protocol for ultrasonographic biophysical profile testing has been previously described.[8] Briefly, ultrasonographic biophysical profile testing does not include a nonstress test (ie, the highest score was 8/8). All biophysical profile testing is done at our affiliate imaging center, Carnegie Imaging for Women, PLLC, by Registry for Diagnostic Medical Sonography–certified ultrasonographers under the supervision of maternal–fetal medicine specialists. An abnormal ultrasonographic biophysical profile is defined as oligohydramnios (amniotic fluid index less than 5 cm) or a 0 of 2 for fetal breathing, fetal tone, or gross movements in a 30-minute period. In the setting of an abnormal ultrasonographic biophysical profile, the woman is sent to the labor and delivery unit for a nonstress test, prolonged fetal heart rate monitoring, repeat ultrasonographic biophysical profile testing, or delivery, as clinical circumstances dictate. Patients with risk factors for adverse outcomes who also have oligohydramnios are typically recommended delivery after 37 weeks of gestation. Our antenatal surveillance protocol did not change over the study time period.

For each patient, we reviewed our computerized medical record and ultrasound reports. We recorded the indication(s) for antenatal testing, ultrasound data, and pregnancy and delivery outcomes. Gestational age was determined by last menstrual period and confirmed by ultrasonography in all patients. The pregnancy was redated if there was a more than 5-day discrepancy up to 14 weeks of gestation or a more than 7-day discrepancy at 14–20 weeks of gestation. If the pregnancy was the result of in vitro fertilization, gestational age was determined from in vitro fertilization dating.

All ultrasonographic biophysical profile results were reviewed as well as all follow-up testing performed for an abnormal result. We calculated the test-positive rate per woman (defined as the percentage of women with an abnormal ultrasonographic biophysical profile at any time), the test-positive rate per ultrasonographic biophysical profile (defined as the percentage of abnormal ultrasonographic biophysical profiles per total ultrasonographic biophysical profiles in the population), the percentage of women delivered for an abnormal ultrasonographic biophysical profile, and the incidence of intrauterine fetal death in the population (the false-negative rate). We also calculated a false-positive rate, defined as an abnormal ultrasonographic biophysical profile that did not lead to intrauterine fetal death or immediate delivery. We repeated these results, excluding women who underwent ultrasonographic biophysical profile solely for the indication of inherited thrombophilia, which is not an ACOG indication for antenatal testing. All results were reported as percentages with 95% CIs.[9]

This project was approved by the Biomedical Research Alliance of New York institutional review board.

RESULTS

Nine hundred eighty-five women met inclusion criteria, undergoing a total of 3,981 ultrasonographic biophysical profiles for an average of four ultrasonographic biophysical profiles per woman (range 1–11). The characteristics of the population, the distribution of number of ultrasonographic biophysical profiles, and the indications for antenatal testing are shown in Table 1. Inherited thrombophilia was the most common indication for ultrasonographic biophysical profile (44.0%) followed by a history of intrauterine fetal death (36.6%). Two hundred forty-eight (25.2%) of women had more than one indication for testing.

Testing outcomes for the ultrasonographic biophysical profiles are shown in Table 2. There was a low test-positive screen rate of ultrasonographic biophysical profiles, both per ultrasonographic biophysical profile and per woman. Overall, there were 17 abnormal tests of the 3,981 ultrasonographic biophysical profiles that were performed, yielding a positive rate per ultrasonographic biophysical profile of 0.4% (95% CI 0.3–0.7%). One woman had two abnormal ultrasonographic biophysical profile results, so there were 16 women with abnormal ultrasonographic biophysical profiles, yielding a test-positive rate per woman of 1.6% (95% CI 1.0–2.6%). Thirteen of these 16 women were delivered after an abnormal ultrasonographic biophysical profile result. Therefore, the delivery rate per abnormal ultrasonographic biophysical profile was 13 of 17 (76.5%, 95% CI 53–90%). In the total population, the number of women delivered for an abnormal ultrasonographic biophysical profile was 13 of 985 (1.3%, 95% CI 0.8–2.3%). Of the 13 women delivered after an abnormal ultrasonographic biophysical profile, four women were delivered for a nonreassuring fetal heart tracing on a reflex nonstress test, six women were delivered for oligohydramnios, and three women were delivered for a ultrasonographic biophysical profile score of 4 of 8 or lower. The other three women with abnormal ultrasonographic biophysical profiles all had normal follow-up nonstress test results and were continued on the ultrasonographic biophysical profile protocol

Table 1. Demographics and Indications for Antenatal Testing

Patient Characteristic	Value
Maternal age (y)	33.5±5.7
Parity	
Nulliparous	192 (19.5)
1	64 (6.5)
2	70 (7.1)
3 or more	659 (66.9)
Gestational age at delivery (wk)	38.6±6.6
Birth weight (g)	3,175±544
5-min Apgar score less than 7	20 (2.0)
Mode of delivery	
Vaginal	653 (66.3)
Forceps or vacuum	24 (2.4)
Cesarean (labored)	119 (12.1)
Cesarean (scheduled)	189 (19.2)
No. of ultrasonographic BPPs—total	
1	83 (8.4)
2	140 (14.2)
3	190 (19.3)
4	160 (16.2)
5	197 (20.0)
6	121 (12.3)
7 or more	94 (9.5)
No. of ultrasonographic BPPs	4.0±1.8
	4 (3–5)
Indication for testing*	
Inherited thrombophilia	433 (44.0)
History of fetal demise	361 (36.6)
Hypertension	146 (14.8)
Diabetes	128 (13.0)
Lupus or renal disease	64 (6.5)
Antiphospholipid antibody syndrome	61 (6.2)
Isoimmunization	29 (2.9)
Congenital heart disease	17 (1.7)
Hyperthyroidism	16 (1.6)
Sickle cell disease	4 (0.4)

BPP, biophysical profile.
Data are mean±SD, n (%), or median (interquartile range).
* Total percentages are greater than 100% because several women had more than one indication.

Table 2. Testing Outcomes for the Ultrasonographic Biophysical Profile

Outcome	n/N (%)	95% CI
Abnormal ultrasonographic BPPs/woman	16/985 (1.6)	1.0–2.6
Abnormal ultrasonographic BPPs/ultrasonographic BPP	17/3,981 (0.4)	0.3–0.7
Delivered for abnormal ultrasonographic BPP	13/985 (1.3)	0.8–2.3
False-positive ultrasonographic BPP*	3/3,981 (0.1)	0.0–0.2
Intrauterine fetal demise (false-negative rate)	3/985 (0.3)	0.1–0.9

BPP, biophysical profile.
* False-positive ultrasonographic BPP=abnormal ultrasonographic BPP that did not lead to an intrauterine fetal death or immediate delivery.

until delivery. None of these women had a repeated abnormal ultrasonographic biophysical profile over the remaining course of their pregnancy and they all ultimately had uncomplicated deliveries. The false-positive rate, defined as an abnormal ultrasonographic biophysical profile that did not diagnose an intrauterine fetal death or lead to delivery, was therefore 3 per 3,981 (0.1%; 95% CI 0.0–0.2%).

There was a low rate of intrauterine fetal death in this population; three women had an intrauterine fetal death over the course of the study period; therefore, the incidence of intrauterine fetal death (false-negative rate) was 3 per 985 (0.3%; 95% CI 0.1–0.9%). Details of the intrauterine fetal deaths are shown in Table 3. Two of the women with intrauterine fetal deaths had an inherited thrombophilia; both women also developed fetal growth restriction and were being monitored with ultrasonographic biophysical profiles as well as umbilical artery Doppler studies. In both cases, the ultrasonographic biophysical profiles and Doppler studies were normal 7 days before the diagnosis of fetal demise. One intrauterine fetal death occurred at 34 3/7 weeks of gestation and the other occurred at 38 4/7 weeks of gestation. The third case of intrauterine fetal death occurred in a woman with class B diabetes at 35 5/7 weeks of gestation. This woman had a normal ultrasonographic biophysical profile 6 days before the diagnosis of intrauterine fetal death.

In regard to the test sensitivity, if all 13 women delivered for an abnormal ultrasonographic biophysical profile were considered to have a form of fetal compromise, and the three women with intrauterine fetal deaths also had fetal compromise, there would be a total of 16 women with fetal compromise. Thus, the sensitivity of the ultrasonographic biophysical profile would be 13 of 16 cases of fetal compromise identified by the ultrasonographic biophysical profile, which would indicate a sensitivity of 81%.

We repeated this analysis excluding 284 women who had ultrasonographic biophysical profiles exclusively for the indication of inherited thrombophilia and obtained similar results. In this population of 701 women (2,832 ultrasonographic biophysical profiles), there was one case of intrauterine fetal death; therefore, the incidence of intrauterine fetal death (false-negative rate) was 1 per 701 (0.1%; 95% CI 0.0–0.8%).

Table 3. Details of Women With Fetal Demise

Gestational Age at Fetal Demise (wk)	Indications for Testing	Details
34 3/7 wk	Inherited thrombophilia	Factor V Leiden mutation, mild fetal ventriculomegaly, fetal growth restriction (7%); normal ultrasonographic BPP and umbilical artery Dopplers 1 wk before diagnosis of fetal demise
38 4/7 wk	Inherited thrombophilia	Advanced maternal age, factor V Leiden mutation, fetal growth restriction (9%); normal ultrasonographic BPP and umbilical artery Dopplers 1 wk before diagnosis of fetal demise
35 5/7 wk	Diabetes	Class B diabetes; normal ultrasonographic BPP 6 d before diagnosis of fetal demise

BPP, biophysical profile.

The other testing results were similar to the results in the overall population (Table 4).

DISCUSSION

In this study, we found that among women with preexisting medical conditions who undergo routine antepartum testing with ultrasonographic biophysical profile, the incidence of intrauterine fetal death, or the false-negative rate, was low (0.3% overall, or 3/1,000, and 0.1%, or 1/1,000 excluding women with inherited thrombophilia). In this population, we found that ultrasonographic biophysical profiles have a low positive screen rate (0.4% per test and 1.6% per woman) and a very low false-positive rate (0.08%). These data are comparable with nonstress tests, which are reported to have a false-negative rate of 0.19% (1.9/1,000)[3] and a full biophysical profile with a false-negative rate of 0.08% (0.8 per 1,000).[3] It is uncertain whether these reported false-negative rates should be compared with one another given the different populations in whom they were used, but they are of the same order of magnitude. Based on our data, the ultrasonographic biophysical profile appears to be a useful tool for antepartum testing among women who are at high risk for intrauterine fetal death.

Table 4. Testing Outcomes for the Ultrasonographic Biophysical Profile, Excluding Women Whose Only Indication for Testing Was Inherited Thrombophilia

Outcome	n/N (%)	95% CI
Abnormal ultrasonographic BPPs/woman	9/701 (1.3)	0.7–2.4
Abnormal ultrasonographic BPPs/ultrasonographic BPP	10/2,832 (0.4)	0.2–0.6
Delivered for abnormal ultrasonographic BPP	6/701 (0.9)	0.4–1.8
False-positive ultrasonographic BPP*	3/2,832 (0.1)	0.0–0.3
Intrauterine fetal demise (false-negative rate)	1/701 (0.1)	0.0–0.8

BPP, biophysical profile.
* False-positive ultrasonographic BPP=abnormal ultrasonographic BPP that did not lead to an intrauterine fetal death or immediate delivery.

Since the biophysical profile was developed and validated by Manning et al in the 1980s,[10] there have been numerous studies assessing the positive predictive values of various components of the biophysical profile. Vintzileos et al[11] found that the nonstress test alone had sensitivity and specificity of 100% and 76%, respectively, whereas the combination of the nonstress test and fetal breathing movements had sensitivity and specificity of 100% and 92%, respectively. In a randomized controlled study by Manning et al,[12] the authors compared complete biophysical profiles with nonstress tests alone; the biophysical profiles were found to be more predictive of low Apgar scores than the nonstress test. A more recent Cochrane meta-analysis compared the traditional biophysical profile with the nonstress test and found no significant differences in neonatal outcomes including perinatal death, Apgar scores less than 7, and cesarean delivery.[13] However, this meta-analysis was limited by small sample size and heterogeneity of existing studies. Finally, a study by Manning et al[14] assessed a modified version of the biophysical profile, in which the nonstress test was only selectively used in cases of abnormal ultrasound-monitored variables. When this modification was implemented, only 2.7% of women required a follow-up nonstress test. This study found that in measurement of gross and corrected perinatal mortality, the nonstress test did not produce a measurable decrease in test accuracy. This study, in which the nonstress test was used only when one or more abnormal ultrasonographic variables were identified, supports our clinical protocol. In contrast to our study, however, Manning et al initiated the ultrasonographic biophysical profile at 36 weeks of gestation or greater,

included singleton and twin gestations, and included women who underwent antepartum surveillance for both maternal and fetal indications.

As with Manning et al, we found a very low rate of abnormal ultrasonographic biophysical profiles that required reflex nonstress testing. In fact, although 16 of the 985 women in our cohort had an abnormal ultrasonographic biophysical profile, only seven of these women underwent nonstress testing; the other nine women were delivered based on the results of the ultrasonographic biophysical profile alone. Three women with abnormal ultrasonographic biophysical profiles had a reassuring nonstress test right afterward, which allowed delivery to be delayed. This is consistent with the low false-positive rate that has been seen in ultrasonographic biophysical profiles for twin pregnancies.[5] The reflex application of the nonstress test, therefore, may provide improved sensitivity in equivocal cases with the ultrasonographic biophysical profile serving as the primary antenatal screen.

The most common indication for testing in our cohort was inherited thrombophilias. Many patients are referred to our practice for this indication, and many patients with poor obstetric histories have thrombophilia testing done by outside health care providers before joining our practice. The indication of inherited thrombophilia was included in our primary analysis, because our practice routinely initiates weekly ultrasonographic biophysical profiles at 32 weeks of gestation for these women. The American College of Obstetricians and Gynecologists, however, does not currently list inherited thrombophilia as an indication for antepartum testing.[3] Studies on the association between isolated inherited thrombophilia and intrauterine fetal death have shown conflicting results. The European Prospective Cohort on Thrombophilia found a significantly increased risk for stillbirth at greater than 28 weeks of gestation among women with antithrombin and protein S deficiencies.[15] Other studies, however, found no association between inherited thrombophilia and unexplained third-trimester intrauterine fetal death.[16,17] Despite the conflicting data, expert opinions suggest weekly fetal assessment beginning 36 weeks of gestation or greater in this population given that there may be a small increased risk for stillbirth in pregnant women with thrombophilia.[18] Additionally, these authors suggest that, if obstetric complications are present, fetal surveillance should be initiated earlier. In this study, we found that two of the three intrauterine fetal deaths in our cohort occurred in women with isolated thrombophilia; however, both of these pregnancies also had suspected fetal growth restriction before demise. Our study does not attempt to answer the question of whether isolated thrombophilias are an indication for antenatal testing in all women or a subset of these women. Also, because we do not routinely test for inherited thrombophilias, our population with this diagnosis is a selected population, typically with poor obstetric histories or other complications that prompted a health care provider (in our practice or elsewhere) to order these tests. When we restricted our analysis to only ACOG indications for antepartum testing, excluding women with isolated inherited thrombophilia, we found similar results; there was a very low test-positive and false-positive rate for ultrasonographic biophysical profiles and low rate of intrauterine fetal death in this high-risk group.

Our study is limited by its retrospective design and a low intrauterine fetal death rate. Although a randomized controlled trial comparing ultrasonographic biophysical profiles with complete biophysical profiles (including the nonstress test) or the nonstress test alone is possible, as demonstrated by our data, intrauterine fetal death is a rare event even in a group of women at high risk for this outcome. Thus, such a study would require a very large sample size. Additionally, no long-term follow-up was available to determine the potential effect of transient hypoxemic events as they relate to biophysical profile scores. We are also limited by patient compliance. Although our protocol is to initiate ultrasonographic biophysical profiles at 32 weeks of gestation and continue weekly, not every patient makes every appointment. This could limit our results. However, our data should provide a pragmatic representation of how the ultrasonographic biophysical profile performs in a true clinical practice, as opposed to a research protocol, which may have improved compliance. A substantial advantage of our study includes the relatively large cohort of patients, a standardized protocol for testing, which occurred at a single ultrasound unit with maternal-fetal medicine specialists reviewing the findings.

In conclusion, in women with preexisting medical conditions that place them at higher risk for fetal demise, ultrasonographic biophysical profiles can be used for antenatal testing. There was a very low rate of intrauterine fetal death in this population that is otherwise at high risk for this outcome. There was also a low test-positive and false-positive rate for ultrasonographic biophysical profiles, indicating that few women required reflex nonstress tests and women were able to avoid unnecessary testing and delivery. We believe that this supports the use of the

ultrasonographic biophysical profile with reflex nonstress testing as a screening strategy, which may be as effective an approach as the traditional biophysical profile or nonstress test alone with lower use of nursing time and cost for determining fetal well-being.

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