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Antenatal Testing – A Reevaluation:

Executive Summary of a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Workshop

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Abstract

In August 2007, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institutes of Health Office of Rare Diseases, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics cosponsored a 2-day workshop to reassess the body of evidence supporting antepartum assessment of fetal well-being, identify key gaps in the evidence, and formulate recommendations for further research. Participants included experts in obstetrics and fetal physiology, and representatives from relevant stakeholder groups and organizations. This article is a summary of the discussions at the workshop, including synopses of oral presentations on the epidemiology of stillbirth and fetal neurological injury, fetal physiology, techniques for antenatal monitoring, and maternal and fetal indications for monitoring. Finally, a synthesis of recommendations for further research compiled from three breakout workgroups is presented.

Since the development of technologies for electronic fetal heart rate monitoring in the 1970s, and with increasing sophistication of ultrasound and Doppler imaging, an array of techniques for antenatal assessment of fetal well being have been introduced into clinical practice. The primary goal of antenatal testing is to identify fetuses at risk for intrauterine injury or death, so that these adverse outcomes can be prevented. Despite widespread use of these technologies, however, there is limited evidence to guide their appropriate application, or to demonstrate their effectiveness at improving perinatal outcomes.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), along with cosponsors, the NIH Office of Rare Diseases, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics, held a workshop on antepartum fetal monitoring on August 27-28, 2007 to critically assess the existing evidence and identify key gaps in knowledge. Experts were invited to summarize the current state of the art in antenatal testing methodology and indications, and to identify pressing research needs. Evidence for a number of important issues was reviewed, including the extent to which

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For a list of workshop participants, see the Appendix online at http://links.lww.com/xxx.

antenatal testing decreases fetal death and long term neurological disability and how antenatal testing impacts gestational age at delivery and mode of delivery. This manuscript is an executive summary of the proceedings of the workshop. Detailed manuscripts by the individual attendees, based on their presentations, were collectively published in a recent issue of *Seminars in Perinatology* (1).

The ultimate goal of antepartum fetal monitoring is to improve perinatal outcome, specifically by decreasing stillbirth and longer term neurologic impairments such as injury to the fetal central nervous system. The rate of stillbirth is 6.2/1000 live births and fetal deaths in the U.S., accounting for more than 55% of perinatal mortality (2). Injury to the fetal central nervous system (CNS) is expressed after delivery in a number of clinical entities and syndromes with cerebral palsy the most common. In contrast to stillbirth, where rates have declined, rates of cerebral palsy have been increasing, primarily due to increased survival of low birth weight and premature infants (3). It is widely held that 90% or more of neonatal encephalopathy cases arise prior to the onset of labor (4), but most antenatal causes of CNS injury are not detected during routine prenatal care (5).

Both stillbirth and cerebral palsy have been associated with extremes of maternal age and parity, maternal obesity, African American race, prenatal smoking, maternal medical disease, use of assisted reproductive technologies, previously affected pregnancy, fetal anomalies, multiple pregnancy, fetal growth restriction, and male fetal sex (6). These similarities in risk factors suggest that fetal CNS injury and stillbirth may share a common pathway. Some authors have postulated that observed trends in decreasing stillbirth rates may be contributing to increasing cerebral palsy rates, i.e. neurologically injured fetuses that would have previously succumbed to in utero death now survive with permanent neurological impairment.

Fetal hypoxia and acidosis represent the final common pathway to fetal injury and death in many high risk pregnancies (7). The basis for antepartum testing relies on the premise that the fetus whose oxygenation in utero is challenged will respond with a series of detectable physiologic adaptive or decompensatory signs as hypoxemia or frank metabolic acidemia develop. In one adaptive response to hypoxemia, blood flow is redirected to the brain, heart, and adrenals with subsequent decreased renal perfusion and fetal urine production, which may result in decreased amniotic fluid volume. Fetal movement is an indirect indicator of central nervous system integrity and function (8). During acute hypoxemia, fetal movements decrease, as the fetus attempts to conserve energy. Loss of fetal movement raises concern for ongoing central nervous system hypoxia and injury. A chemoreceptor response to hypoxemia leads to vagally-mediated reflex slowing of the fetal heart rate (FHR), which may appear clinically as late decelerations associated with uterine contractions.

A number of investigators have described sequences of measurable changes in fetal blood flow and biophysical parameters that occur as placental insufficiency worsens and fetal hypoxemia and acidemia develop (9;10). Although the precise sequences of observed characteristics differ slightly in these reports, a general pattern of fetal response to intrauterine challenge emerges (Figure 1). Loss of FHR reactivity and abnormal blood flow in the umbilical artery are often the earliest signs of fetal compromise. Sequential changes in other fetal vessels are detectable next, followed by abnormalities in biophysical parameters such as fetal breathing movements, amniotic fluid levels, fetal body movements, and fetal tone. Not all fetuses exhibiting the full range of these findings, however, will exhibit significant metabolic acidosis at birth. In a group of 34 liveborn infants with intrauterine growth restriction delivered because of progressive deterioration in Doppler and biophysical parameter assessments, while all had abnormal arterial cord blood pH (median 7.23, range 6.95 – 7.29), the median base excess was -4.6 (range −14.5 to 0.9), and 3/34 (8.8%) had an Apgar < 7 at 5 minutes (11).

Antenatal Testing Methodologies

Fetal movement counting

In the normal fetus, fetal movements are first perceptible at 17 – 20 weeks and reach peak frequency at or before 38 weeks. Fetal movement decreases in response to hypoxemia, making formalized maternal assessment of fetal movements a potentially simple method of monitoring fetal oxygenation and well being. Results of trials of routine fetal movement assessment for reduction of stillbirth have been mixed. In a randomized trial conducted in Denmark (12), fetal movement counting (FMC) was associated with a 73% reduction in avoidable stillbirths (RR 0.27, 95% CI 0.08-0.93). However, a subsequent large (N=68,654) international trial showed no difference in potentially avoidable late fetal deaths between women who were instructed to count routinely and controls (difference in mean rate -0.06/1000, 95% CI −0.76 to 0.64) (13). The results of these trials are difficult to compare because of methodologic differences, particularly in how women were instructed to count movements and how decreased fetal movement was defined. Though the “count to 10” method (14) is frequently employed, it is not clear from the existing evidence whether there is a specific fetal movement threshold or “alarm limit” below which fetal risk is increased. Some authors suggest that a more important predictor may be an overall maternal sense that fetal activity is reduced, and that any such report warrants further evaluation (15). A recent systematic review (16) concluded that there is insufficient evidence to recommend routine fetal movement counting to prevent stillbirth.

Cardiotocographic techniques: contraction stress test, nonstress test (Table 1)

The contraction stress test (CST) is based on the premise that uterine contractions transiently restrict oxygen delivery to the fetus and that a hypoxic fetus will demonstrate recurrent late decelerations. The rate of antepartum stillbirth within one week of a negative CST (i.e., the false negative rate) is 0.04% (17); however, of positive tests, up to 30% have been reported to be false positive (that is, patients tolerate labor without FHR changes indicating intervention.) (18). Drawbacks to the CST include the need to stimulate contractions and the fact that inducing contractions is contraindicated in a number of conditions (e.g., placenta previa). A less intensive method, the nonstress test (NST), grew from the observations that the presence of two or more fetal heart rate accelerations during a CST most often predicted a negative CST and that absence of accelerations on a baseline FHR tracing was associated with adverse perinatal outcomes (19). The NST false negative rate is about 0.3% (20). Non reactive NSTs have about a 55% false positive rate (i.e., a backup test is normal) (21). NSTs should be performed at least twice weekly (22).

Ultrasonographic assessments: Amniotic fluid volume, biophysical profile and modified biophysical profile (Table 1)

Amniotic fluid volume (AFV) is commonly estimated by either the maximum vertical pocket (MVP) or the 4-quadrant amniotic fluid index (AFI) (23;24). By dye dilution studies, both AFI < 5 cm and MVP <2 cm had poor sensitivity for detecting true oligohydramnios (sensitivity 10% and 5%, respectively). Similarly, AFI > 20 cm and MVP > 8 cm were poor predictors of true polyhydramnios (sensitivity 29% for both) (25). The biophysical profile (BPP) combines the ultrasonographic estimation of AFV and assessments of fetal breathing, body, and reflex/tone/flexion-extension movements with the NST. (26). This test is felt to assess indicators of both acute (NST, breathing, body movement) and chronic (AFV) hypoxia, and the BPP score is linearly correlated with fetal pH (27). The risk of fetal death within one week of a normal biophysical assessment is 1 in 1300 (28). The modified biophysical profile (mBPP) relies on the NST as a measure of acute oxygenation, and the AFI as a measure of longer term oxygenation (29). In a large observational study, the false negative rate was 0.8/1000, but 60% of abnormal modified BPP's are false positive (30).

Doppler velocimetry

Measurement of blood flow velocities in the maternal and fetal vessels gives information about uteroplacental blood flow and fetal responses to physiologic challenges. Of all the antenatal assessment methods, Doppler-based tests have been most rigorously evaluated in randomized trials. The information derived from velocity waveforms in different vessels varies according to the specific vessel assessed (see Table 2).

Uterine artery (UtA)—Failure of adequate trophoblast invasion and remodeling of maternal spiral arteries is characterized by persistent high-pressure uterine circulation and increased impedance to uterine artery blood flow. Elevated resistance indices and/or persistent UtA waveform notching at 22-24w indicate reduced blood flow in the maternal compartment of the placenta and have been associated with future preeclampsia, fetal growth restriction (FGR), and perinatal death (31). A number of investigators have explored the use of UtA Doppler for third trimester fetal assessment among women with complicated pregnancies (32-34), but its role in this setting has not been clearly defined.

Umbilical artery (UA)—Umbilical artery flow velocity waveforms of normally growing fetuses are characterized by high-velocity diastolic flow, while in growth-restricted fetuses, UA diastolic flow is diminished, absent, or even reversed in severe cases (35). This progressive reduction of UA diastolic flow is associated with worsening destruction of placental villous vasculature (36). In the growth restricted fetus, absent or reversed end diastolic flow is associated with fetal hypoxia (37) and increased perinatal morbidity and mortality (38). In a systematic review of 11 randomized trials enrolling approximately 7000 high-risk patients, the use of Doppler ultrasound was associated with a trend toward decreased perinatal mortality (OR 0.71, 95% CI 0.50 – 1.01) (39). UA Doppler assessments are considered most useful for monitoring of early-onset growth restriction due to uteroplacental insufficiency (40). Several randomized trials have demonstrated that routine UA Doppler screening of all pregnancies does not improve perinatal outcomes (41). Current American College of Obstetricians and Gynecologists (ACOG) practice guidelines support the use of UA Doppler assessments only in the management of suspected intrauterine growth restriction, stipulating that decisions regarding the timing of delivery should be based on UA Doppler results in combination with other tests of fetal well-being (18).

Middle cerebral artery (MCA)—In the compromised fetus, systemic blood flow is redistributed from the periphery to the brain. Doppler measurement of flow velocity in the fetal middle cerebral artery can detect this “brain-sparing effect” and has gained recent attention as an assessment tool. The limited data available currently are mixed.

Fetal veins (umbilical vein, inferior vena cava, ductus venosus)—Blood flow in the umbilical vein is continuous in normal pregnancies after 15 weeks gestation. Pathological states, such as FGR, may be associated with pulsatile flow in the umbilical vein, which is a reflection of cardiac dysfunction against increased afterload. The ductus venosus regulates oxygenated blood in the fetus (42) and is resistant to alterations in flow except in the most severely growth restricted fetuses. Recent evidence suggests that Doppler evaluation of fetal veins combined with arterial assessments is useful for predicting outcomes in growth restricted fetuses (43;44).

Emerging Methods of Fetal Assessment

Fetal physiology assessment

As the fetal central nervous system matures, there are distinctive alterations in fetal physiological and behavioral parameters, such as heart rate patterns, motor activity, and sleep-

wake cycles. One important developmental feature is the increased coupling between fetal movement (FM) and FHR that normally occurs with advancing gestational age and reflects maturation of the parasympathetic and sympathetic components of the fetal autonomic nervous system. The use of a fetal actocardiograph, which electronically records FHR *and* FM, and novel analytic techniques allow computation of time-dependent cross-correlation coefficients between FHR and FM (45). Studies have suggested that high levels of maternal stress (46), preterm birth, and other pregnancy complications (45) are associated with alterations in FM/FHR coupling as well as FHR reactivity (47). Potential impairment or maturational delay of the fetal autonomic nervous system from a variety of insults or exposures may be detected by monitoring movement-related patterns of FHR in combination with FM/FHR coupling measures.

Fetal magnetoencephalography

Aims for direct assessment of fetal cortical and brainstem function. A specialized apparatus incorporating an array of ultrasensitive magnetic field detectors allows noninvasive, direct continuous recording of fetal electro-cortical signals, and can record fetal brain activity in response to auditory and visual stimuli applied to the maternal abdomen (48;49). This technology may contribute to future clinically important assessments of the CNS status of the fetus.

Indications for Antenatal Testing (Table 3)

Diabetes

Historically, insulin-dependent diabetes has been a major contributor to perinatal mortality; however, due to both improved treatment and antepartum monitoring, the stillbirth rate in pregnancies complicated by diabetes now is equivalent to or lower than uncomplicated pregnancies (50). Poorly controlled maternal diabetes is associated with increased perinatal mortality largely related to congenital anomalies and indicated preterm deliveries, but also to sudden unexplained fetal death. Though observational studies have described the use of the NST (51), CST (52), and BPP (53) in management of diabetic pregnancy, no method(s) have been assessed in well-designed clinical trials and it is not clear which method, if any, is superior. There is no evidence supporting routine antepartum fetal assessment in diet-controlled gestational diabetes (54).

Hypertensive Disorders

Maternal hypertension in pregnancy, whether chronic, pregnancy-induced, or a combination, is a risk factor for perinatal death, and is a common indication for antenatal testing (20). There are insufficient data to recommend one testing modality over another, or to make conclusions about when testing should begin and how frequently it should be repeated. Some authorities hold that mild to moderate chronic hypertension in the absence of growth restriction or superimposed preeclampsia is not an indication for routine fetal surveillance (55), and a recent systematic review concluded that benefits and harms of routine antenatal assessment in women with chronic hypertension cannot be determined with current evidence (56). No randomized trials have assessed the best method for antenatal testing in the preeclamptic patient for whom delayed delivery is desired. The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy has recommended daily fetal movement assessment, and weekly nonstress tests and/or biophysical profiles for patients with mild preeclampsia before term (55). If fetal growth restriction or decreased AFV are present, testing is recommended twice weekly. Daily fetal cardiotocographic or ultrasound surveillance may be useful in conservative management of severe preterm preeclampsia (57).

Fetal Growth Restriction

FGR is a well-recognized risk factor for fetal death. Abnormalities in Doppler velocimetry indices may help distinguish between fetal growth restriction due to placental insufficiency, in which impedance indices tend to be increased, and growth restriction from other causes (e.g. congenital infection) or constitutional smallness, which are less frequently associated with increased impedance to blood flow (58;59). There are no data from randomized trials indicating the optimal mode and frequency of antenatal testing of the fetus with growth restriction. Given the limitations in predictive value, timing delivery based on results of antenatal testing in preterm FGR presents a particular problem, as the risks of fetal loss must be balanced against the risks of iatrogenic prematurity.

Multiple pregnancy

The greater prevalence of maternal risk factors (e.g. advanced maternal age, preterm labor, preeclampsia) and fetal risk factors (e.g. abnormal growth, abnormal placentation, congenital anomalies) contribute to higher perinatal mortality rates in multiple gestations than in singletons. Population based evidence indicates that the lowest risk for intrauterine death in multiple gestations occurs at 37-38w (60). Chorionicity is an important consideration in the assessment of risk, with higher rates of adverse outcomes among monochorionic twins. Limited data specific to twin pregnancy suggest that weekly simultaneous NSTs (60), BPPs (61), mBPPs, and UAD, alone or in combination, (62) may be of benefit in predicting outcomes in twin pregnancies. There are scant data to indicate the gestational age at which testing should start; some suggest that fetal surveillance among diamniotic-dichorionic twins with concordant growth may not be needed before 38 weeks. There is insufficient evidence to support specific recommendations for any antenatal testing strategy in triplets and higher-order multiples.

Amniotic fluid abnormalities

Abnormalities of AFV have long been viewed as risk factors for poor perinatal outcomes (63;64), although this concept has recently been called into question (65). Polyhydramnios (AFI > 24 OR MVP > 8) and oligohydramnios (AFI < 5 or MVP < 2 cm) each frequently coexist with other maternal or fetal problems, such as congenital anomalies, diabetes, hypertension, postterm pregnancy, and fetal growth restriction. There is some controversy over whether isolated oligohydramnios (66) or polyhydramnios (67) near term is associated with adverse pregnancy outcomes. In a large retrospective study, approximately 40% of repeat assessments of oligohydramnios (AFI ≤5 cm) revealed AFI > 5 cm within 3 – 4 days (68). There are few data on which to base recommendations for antenatal testing in pregnancies with abnormalities of AFV.

Preterm premature rupture of membranes (PPROM) is associated with oligohydramnios and subclinical intrauterine infection. The goal of antenatal testing in this setting is early recognition of chorioamnionitis necessitating delivery. Most experts recommend daily antenatal testing in patients with PPROM, either with the NST (69) or the BPP (70).

Roughly 40% of third-trimester polyhydramnios cases diagnosed by ultrasound have normal or near-normal AFV on subsequent assessments; outcomes in these cases are generally good (71). Persistent polyhydramnios is associated with poorer pregnancy outcomes, including fetal anomalies, maternal diabetes, and perinatal death (71); these pregnancies may benefit from antenatal surveillance, but there are little data to support specific methodologies (67).

Postterm pregnancy

Postterm pregnancy is associated with increased fetal mortality and neonatal seizures, especially if growth restriction is present (72). The optimal gestational age at which to initiate

testing has not been established. Some investigators have recommended ≥ 41w, (73;74). Because adverse pregnancy outcomes increase after 40w, ACOG guidelines support initiating antenatal assessment after 40 w, though there are no randomized trial data to show that testing improves perinatal outcomes (74). Several investigators have evaluated the mBPP for monitoring postterm pregnancy (30;75).

Oligohydramnios in postterm pregnancy is associated with poorer outcomes. However, recent studies have questioned the utility of AFV estimation as an independent predictor of adverse outcomes in prolonged pregnancies (76;77). Use of the AFI versus the MVP may increase the diagnosis of oligohydramnios without impacting perinatal outcome (78). Twice-weekly assessment of AFV is commonly recommended for patients at ≥ 41 weeks gestation (74).

Elevated risk in postdates pregnancy is related to impaired placental gas exchange, therefore Doppler assessments of placental circulation would not be expected to be helpful (40). Correlation of UA Doppler results with outcome is poor (79) and sensitivity is low. There is no clear role for Doppler velocimetry in monitoring postterm pregnancies given the existing evidence.

History of prior stillbirth

A history of previous stillbirth is associated with a two- to tenfold increased risk of fetal death in subsequent pregnancy, depending in part on the etiology of the previous loss (80). Previous stillbirth has long been considered an indication for antepartum testing (81); however, there are no randomized trial data and scant other data on when to initiate testing, or whether antepartum surveillance by any method is effective at reducing the risk of recurrent stillbirth. Some authors recommend initiating testing at 34 weeks, or 1 week prior to the previous loss (30). Weeks, et al. (82) followed 300 otherwise healthy patients for whom history of prior stillbirth was the only indication for antenatal testing with weekly CSTs or semiweekly mBPPs. In this cohort, there was one perinatal death (recurrent stillbirth 3 days after a negative CST and <24 hours after a reactive NST), and 13.6% of patients were delivered for positive or equivocal fetal testing results. All 3 of the patients whose first abnormal test result occurred at <32w were delivered at term without complications. Additionally, there was no association between gestational age at previous stillbirth and the incidence of an abnormal test or cesarean delivery for fetal distress. The authors concluded that it is reasonable to initiate antenatal testing for history of stillbirth at 32 weeks. Comparing the recurrent fetal death rate in this study (1/300 or 3.3/1000) to that in another relatively low-risk population (19.0/1000, (83)), suggests that serial CSTs or mBPPs may reduce the risk of recurrent stillbirth, but this has not been rigorously tested.

Decreased fetal movement

By a number of definitions, decreased fetal movement (DFM) has been associated with adverse pregnancy outcomes such as congenital malformations (84), FGR (85), preterm delivery (86), and perinatal death (87). However, not all (88) studies link DFM to adverse outcome. DFM requires evaluation (18), but there are no randomized trials and little other data to support a specific protocol for such evaluation. Most authors (8) recommend an NST at a minimum. ACOG/AAP Guidelines for Perinatal Care recommend an NST and AFI for evaluation of DFM (89). Patients in whom an NST and ultrasound/AFV assessment are normal do not appear to require further testing (90). There is no clear evidence that adding UA or UtA Doppler assessments in the evaluation of DFM in otherwise low-risk women improves perinatal outcomes (91).

Newer indications for antenatal testing

The ACOG practice bulletin on antepartum fetal surveillance suggests that antepartum testing may be appropriate for any "pregnancies in which the risk of antepartum fetal demise is increased," including the conditions described (18) (Table 3). Recent research has highlighted increased stillbirth risk for a number of additional conditions, including: advanced maternal age (92), nulliparity (93), grand multiparity (94), obesity (95), conception with assisted reproductive technologies (96), hereditary and acquired thrombophilias such as factor V Leiden mutation (97), and abnormalities in first and second trimester serum screening results (98; 99). Whether a program of antenatal testing in women with these risk factors can reduce the incidence of stillbirth is unknown.

Benefits and costs of antenatal testing

The gaps in the evidence regarding the efficacy of antepartum testing in preventing fetal death or injury make it difficult to assess the large-scale benefits of antepartum testing in general. Limitations of the existing evidence also prevent a comprehensive understanding of the costs of antenatal fetal surveillance. Potential costs include the actual dollars spent on tests and their interpretation; opportunity costs of patients' and practitioners' time spent in testing; and maternal and infant morbidity (or even mortality), e.g. from labor inductions, cesarean deliveries, or iatrogenic prematurity, especially given the chances for false positive tests. Very little is known about the effects of antenatal testing on maternal mental states—does testing provoke anxiety or rather offer reassurance? How these potential costs balance against potential benefits is uncertain.

Challenges and Opportunities

The existing literature on the ideal use of antenatal testing and its benefit in reducing fetal death or injury is characterized by a number of overarching limitations. Importantly, much of the existing evidence is observational, and recommendations are often based on expert opinion. There is a clear need for additional randomized trial data; however, conducting well-designed randomized trials could be challenging. For one thing, despite weaknesses in evidence, antepartum testing is an accepted and expected component of prenatal care in many cases, making it difficult or impossible to design definitive trials comparing outcomes among pregnancies assigned to testing versus no testing. Furthermore, even among pregnancies at increased risk, stillbirth and CNS injury are rare outcomes, and multiple potential confounding factors must be taken into account; it is thus difficult to conduct adequately powered trials. In attempts to overcome this barrier, many investigators have assessed more common surrogate endpoints (e.g., cesarean delivery for fetal distress or meconium staining), but it is not clear which, if any, are most appropriate. Thus, for many antenatal testing strategies, there are few data directly indicating that their use reduces rates of fetal death or long-term neurological impairment. It is worth considering whether the development of alternate definitions of false-negative and false-positive tests would serve to advance research in the field.

To date, most studies on the predictive value of antenatal testing methods have been conducted in heterogeneous groups of "high-risk" pregnancies (100) (Table 3). It may not be appropriate to generalize one testing methodology to all conditions. Rather, testing protocols should be specific to the underlying risk condition prompting the assessment. Effectiveness of antenatal fetal testing in preventing stillbirth may be improved by targeting specific testing modalities to specific pathophysiologic process. Kontopoulos and Vintzileos (40) reported that condition-specific fetal testing in 12,766 high risk pregnancies at their institution resulted in a fetal death rate of 1/3191, a threefold decrease from rates where the same assessments are used without condition-specificity. Persistent gaps in our understanding of fetal disease processes and their progression limit further condition-specific application and interpretation of tests.

Condition-specific testing, however, cannot, however, fully address the scope of potentially preventable fetal death and injury. As many as 50% of late fetal deaths occur in women without identifiable risk conditions (14). It is especially difficult to design studies and strategies for using antenatal testing to prevent these unexpected losses. Some method of maternal assessment of fetal movement appears to be a promising candidate for a universal screening test, but it is not clear that this or any of the other existing methodologies can have an impact in these pregnancies at subclinical risk, at least not in the ways that they are currently applied.

For the most part, studies of antenatal testing have focused on stillbirth prevention— the body of research examining long term outcomes among surviving infants is substantially underdeveloped. Future work should adopt a wider view to investigate the role of antepartum testing in prevention of disability in addition to prevention of perinatal death. Such research must employ long term, high quality follow up, evaluate other composite short and long term outcomes (neurologic injury, neurodevelopmental outcomes, etc), and must also account for environmental and external influences after delivery.

Conclusion: Defining a Research Agenda

Priority areas for future research are highlighted in Box 1. For all areas of research, workshop participants stressed the need for well-designed randomized controlled trials whenever appropriate. For example, it would be both feasible and important to conduct trials comparing the effectiveness of different combinations of primary and secondary assessment techniques on improving perinatal outcomes.

Researchers should evaluate newer systems of test interpretation on a number of levels. For example, perhaps the binary classification of NST results is an oversimplification. The implications of antepartum testing results for individual patients may be improved if they are considered in combination with pretest odds and likelihood ratios. Determination of pretest odds may be based on multiple factors, such as severity of underlying disease, socioeconomic status, previous obstetric history, obesity, and tobacco use.

Further attention to developing evidence-based testing intervals and appropriate ages to initiate testing is needed. There is little evidence to allay concerns that early onset of antepartum fetal surveillance may lead to situations in which false positive test results lead to inductions of labor, potentially higher cesarean delivery rates, and iatrogenic prematurity. Clearer data on application and interpretation of antenatal tests in fetuses < 32 weeks gestation is an important research need. A common theme was that future studies should investigate application of testing technologies and strategies specifically targeted to the underlying disease process warranting surveillance. To this end, additional observational studies to better understand placental pathophysiology and fetal reactions to specific maternal disease states are warranted. Randomized trials could compare performance of different testing strategies between groups of women with similar underlying pathology. Attention should be given to development of preconceptional and interconceptional practices that may mitigate the risk of fetal injury and death.

In summary, participants at the NICHD workshop, *Antenatal Testing: A Reevaluation*, identified numerous gaps in the evidence guiding the clinical application of most antepartum assessments commonly in use today. Existing data are primarily observational, and neglect some potentially important questions, such as the appropriate gestational age to initiate testing, the adaptations needed for assessment of infants at lower gestational ages, the optimal frequency of testing, and the targeting of technologies to underlying pathophysiology. Though there are challenges to designing and conducting adequately powered studies of antenatal testing strategies, further research is clearly needed.

Box 1: Recommendations for future research

Epidemiology of stillbirth and cerebral palsy

- Development of national active surveillance programs
- Routine thorough etiologic investigations after stillbirth
- Emphasize long term neurodevelopmental followup

Fetal/placental pathophysiology

- Enhance knowledge of placental dysfunction
- Observational studies of changes in fetal physiology and test results by specific disease processes
- Understand possible subtypes of fetal growth restriction
- Definitions and significance of amniotic fluid abnormalities

Fetal movement assessment

- Improve discrimination between normal and abnormal fetal movement
- Develop effective algorithm for fetal movement assessment
- Identify role in universal screening or as adjunct assessment

Fetal testing technologies

- Identify most appropriate method for primary surveillance and backup testing
- Establish best testing intervals
- Further research on ages at which to initiate testing
- Best methodologies in the fetus <32w
- Benefits of matching testing methods to indication and specific pathophysiology
- Development of risk profiles incorporating testing results and additional pregnancy exposures and characteristics
- Evaluate combinations of assessments
- Research and development of technologies for early identification of the fetus at risk for neurologic injury

Indications for antenatal testing

- Role of antenatal surveillance in well-controlled diabetes
- Utility of Doppler ultrasound in management of preeclampsia
- Use of customized growth percentiles for evaluation of fetal growth and implications for antenatal testing
- Further study of testing in twins and higher-order multiples
- Investigate new indications for testing: advanced maternal age, obesity, nulliparity, thrombophilia, assisted reproduction, tobacco use, previous poor pregnancy outcome

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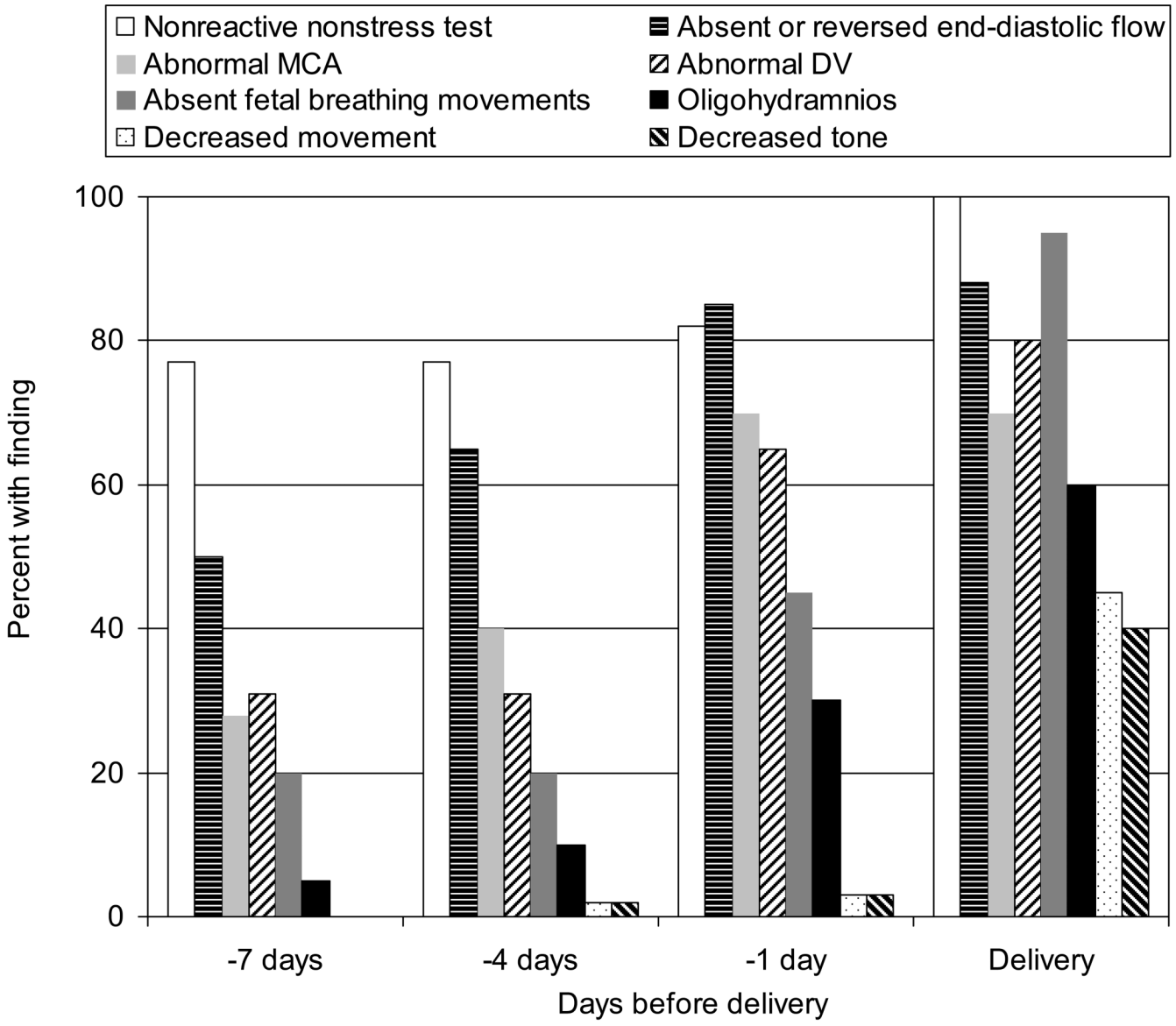

Figure 1.
Progression of Doppler and biophysical findings in severe fetal growth restriction. NST, nonstress test; absent or reversed end-diastolic flow; MCA, middle cerebral artery; DV, ductus venosus; fetal breathing movements. Data from Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 2001;18:571-7.

Table 1

Antenatal Testing Methodologies

Name	Components	Results/Scoring	False Negative	False Positive	References
Contraction Stress Test (Oxytocin Challenge Test)	• Continuous FHR monitoring • At least 3 contractions of ≥ 40s duration within 10 min	• **Negative**: no late or significant variable decelerations • **Positive:** late decelerations following ≥ 50% of contractions • **Equivocal – suspicious:** intermittent late decelerations or significant variable decelerations • **Equivocal – hyperstimulatory:** decelerations with contractions occurring more frequently than q 2 min. or lasting > 90s • **Unsatisfactory:** < 3 contractions in 10 min. or uninterpretable FHR tracing	0.04%	35 - 65%	(17;101)
Nonstress Test	• Continuous FHR monitoring • FHR accelerations: ≥ 32w: reaching 15 bpm above baseline and lasting ≥ 15s	• **Reactive:** ≥ 2 accelerations within 20 min (may be extended to 40 min) • **Nonreactive:** < 2 accelerations in 40 min	0.2 – 0.65%	55 - 90%	(20-22;102-104)
Biophysical Profile	Presence or absence of 5 components within 30 min: • Reactive NST • ≥ 1 episode of fetal breathing movements lasting ≥ 30s • ≥ 3 discrete body or limb movements • ≥ 1 episode of extremity extension with return to flexion or opening or closing of a hand • Maximum vertical AF pocket > 2 cm or AFI > 5 cm	Each component present is assigned score of 2 points; maximum score is 10/10 • **Normal:** ≥ 8/10 or 8/8 excluding NST • **Equivocal:** 6/10 • **Abnormal:** ≤ 4/10	0.07 - 0.08%	40 - 50%	(28;105;106)
Modified Biophysical Profile	• NST • AFI	• **Normal:** Reactive NST *and* AFI > 5 cm • **Abnormal:** Nonreactive NST *and/or* AFI ≤ 5 cm	0.08%	60%	(30;75;107;108)

Table 2
Doppler assessment of maternal/fetal circulation and clinical information

Vessel examined	Clinical Information
Uterine artery	Maternal (flow resistance to the uterus)
Umbilical artery	Placental (flow resistance to placenta)
Arterial circulation (MCA)	Fetal (fetal adaptation to flow resistance change)
Venous circulation (umbilical vein, inferior vena cava, ductus venosus)	Fetal (fetal cardiac function)

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Table 3

Maternal risk factors and estimated risk of stillbirth, and reported strategies for antepartum fetal surveillance

Condition	Prevalence	Estimated rate of stillbirth	Odds Ratio	GA to initiate testing	Testing mode and schedule	References
All pregnancies	--	6.4/1000	1.0	--	--	(109)
Low-risk pregnancies	80%	4.0 – 5.5/1000	0.86	--	--	(109)
Diabetes						
Treated with diet (A1)	2.5 – 5%	6 – 10/1000	1.2 – 2.2	Not indicated	--	(54;109)
Treated with insulin	2.4%	6 – 35/1000	1.7 – 7.0	A2, B, C, D without HTN, renal disease, or FGR: 32 w	CST/w, midweek NST	(52;109)
				32 w	NST or BPP 2x/w	(110)
				34 w	NST 2x/w + AFI/w	(51)
				R, F: 26w	CST/w, midweek NST	(52)
				Any class with HTN, renal disease, FGR: 26 w	CST/w, midweek NST	(52)
				28 w	NST or BPP 2x/w	(110)
Hypertensive disorder						
Chronic hypertension	6 – 10%	6 – 25/1000	1.5 – 2.7	26 w	NST, AFI 2x/w	(109;111)
				33 w	MBPP 2x/w	(29;112)
				With SLE or FGR or DM or PIH: 26 w	NST, AFI 2x/w	(112;113)
Pregnancy-induced hypertension						
Mild	5.8 – 7.7%	9 – 51/1000	1.2 – 4.0	At diagnosis	MBPP 2x/w	(29;30;109)
Severe	1.3 – 3.3%	12 – 29/1000	1.8 – 4.4	At diagnosis	NST/day with BPP if nonreactive; AFI 2x/w	(57;109)
Growth restricted fetus	2.5 - 10%	10 – 47/1000	7 – 11.8	Suspected: at diagnosis	NST, AFI/w	(113-115)
					UAD 1-2x/w	(18;116)
				Confirmed	MBPP 2x/w	(29;30)
					UAD 1-2x/w	(18;116)
Multiple gestation	2 – 3.5%					
Twins	2.7%	12/1000	1.0 – 2.8	Concordant growth: 32 w	NST, AFI/w	(109;113)
				Discordant growth: at diagnosis	MBPP 2x/w	(30)
Triplets	0.14%	34/1000	2.8 – 3.7	28 w	BPP, 2x/w	(109;117)
Oligohydramnios	2%	14/1000	4.5	At diagnosis	NST, AFI 2x/w	(113;118)
PPROM				At diagnosis	NST/day	(69;119)
					BPP/day	(108;120)
Postterm pregnancy (compared to 40w)						
41w	9%	1.6/1000	1.5	41 w	BPP 2x/w	(72;121;122)
				41 w	MBPP/w	(30)
≥ 42w	5%	2 – 3.5/1000	1.8 – 2.9	42 w	MBPP 2x/w	(30;72;121)
Previous stillbirth	0.5 – 1.0%	9 – 20/1000	1.4 – 3.2	32 w	MBPP 2x/w or BPP/w or CST/w	(29;82;109;120)
				34 w or 1 w prior to previous stillbirth	MBPP/w	(30)
Decreased fetal movement	4 – 15%	13/1000	2.5 – 5.6	At diagnosis	MBPP	(15;29;30;84;109)
SLE	< 1%	40 – 150/1000	6 – 20	26 w	CST, BPP, or NST/w	(109;123)
Renal disease	< 1%	15 – 200/1000	2.2 – 30	30 – 32	BPP 2x/w	(109;124)
Cholestasis of pregnancy	< 0.1%	12 – 30/1000	1.8 – 4.4	34 w	MBPP/w	(30;109)
Advanced maternal age (reference < 35 y)						
35 – 39 y	15 – 18%	11 – 14/1000	1.8 – 2.2	ID	ID	(109)
40 y +	2%	11 – 21/1000	1.8 – 3.3	ID	ID	(109)
Black women compared with white women	15%	12 – 14/1000	2.0 – 2.2	ID	ID	(109)
Maternal age < 20	4%	7 – 13/1000	1.1 – 1.6	ID	ID	(121;125)
Nulliparity	40%	3.8 (Sweden)	1.2 (Sweden)	ID	ID	(93;126)
Very high (10-14) or extremely high (≥ 15) parity	0.1%	14 – 22/1000	2.0 – 2.2	ID	ID	(94)
Assisted reproductive technology	1%	12/1000	2.6	ID	ID	(127)

Condition	Prevalence	Estimated rate of stillbirth	Odds Ratio	GA to initiate testing	Testing mode and schedule	References
Abnormal serum markers						
1st trimester PAPP-A <5th Percentile	5%	9/1000	2.2 – 4.0	ID	ID	(98;128)
2 or more abnormal 2nd trimester quad screen markers	0.1 – 2%	8 – 18/1000	4.3 – 9.2	ID	ID	(99)
Obesity (prepregnancy)						
BMI 25 – 29.9 kg/m^2	21%	12 – 15/1000	1.9 – 2.7	ID	ID	(109)
BMI ≥ 30 kg/m^2	20%	13 – 18/1000	2.1 – 2.8	ID	ID	(109)
Low educational attainment (< 12 y vs. 12 y +)	30%	10 – 13/1000	1.6 – 2.0	ID	ID	(109)
Smoking > 10 cigarettes/day	10 – 20%	10 – 15/1000	1.7 – 3.0	ID	ID	(109)
Thrombophilia	1 – 5%	18 – 40/1000	2.8 – 5.0	ID	ID	(109)
Thyroid disorders	0.2 – 2%	12 – 20/1000	2.2 – 3.0	ID	ID	(109)

GA, gestational age; CST, contraction stress test; w, week; HTN, hypertension; FGR, fetal growth restriction; NST, nonstress test; BPP, biophysical profile; AFI, amniotic fluid index; mBPP, modified biophysical profile; SLE, systemic lupus erythematosus; DM, diabetes mellitus; PIH, pregnancy-induced hypertension; y, years; ID, insufficient data; BMI, body-mass index.