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Comparison of Maternal and Neonatal Outcome Before and After the Availability of a Rapid Assay for Fetal Fibronectin at a Tertiary Level Maternity Hospital

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by

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DEDICATION

To those who believed in me and supported me on this journey.

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ABSTRACT OF THE DISSERTATION

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Doctor of Philosophy in Public Health (Epidemiology)

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Spontaneous preterm birth prior to 37 weeks gestation is a leading cause of neonatal morbidity and mortality. The preterm birth rate in the United States remains higher than in many other westernized countries. The etiology of preterm birth, identification of women at risk, and effective interventions for preterm birth prevention remain public health, research, and clinical challenges.

Fetal fibronectin (FFN), a specific biomarker, seen in cervical and vaginal secretions with disruption of the decidual interface, predicts risk for preterm delivery. The purpose of this retrospective cohort study was to examine whether the availability of clinical FFN testing had an impact on preterm birth, NICU admissions, or use of hospital services. The study compared cohorts seen for assessment of preterm labor symptoms in the six months prior (n=372) to and after (n=390) availability of testing; 215 tests were performed on 183 subjects. Test use increased significantly during the time of test availability, (trend, $p < 0.001$) however, overall test utilization rate remained below 50%. The study failed to demonstrate a reduction in preterm delivery, NICU admission, or hospital admissions. Lack of major significant study findings are likely attributable to insufficient power due to limited test utilization, prolonged implementation time, and lack of procedural policies, which reduced the potential impact of testing on patient care. The test negative predictive value (100%) for delivery within 14 days was consistent with previous findings, however, this did not lead to the reduced hospital admissions seen in previous studies. Findings suggest that implementation of FFN testing in clinical settings takes time and requires more rigorous policies for use to replicate previous research findings. Current practice combines FFN testing with cervical length and consideration of other risk factors, especially a history of preterm birth, to improve diagnostic precision. Use of predictive algorithms using the best evidence and predictive factors for subpopulations may lead to improved diagnostic precision in the future.

CHAPTER 1

INTRODUCTION

Preterm birth, or birth before 37 weeks completed weeks gestation, is a major cause of pregnancy related morbidity and neonatal morbidity and mortality (March of Dimes 2005), and the major obstetrical and neonatal problem in the developed world (Lockwood, Ramin, & Vars, 2009). Identification of women at risk for and prevention of preterm labor are limited by the complex and poorly understood pathways leading to preterm birth.

Recent research has focused on identification of potential biomarkers that may herald the onset of preterm labor or preterm premature rupture of membranes. From a clinical perspective, the optimal biochemical marker would allow identification of women who are or are not at risk of imminent preterm delivery. Even with an accurate diagnosis of preterm labor, the lack of interventions to prolong pregnancy remains a problem (Lockwood et al., 2009).

Presence of fetal fibronectin, a specific biomarker, in the cervical and vaginal secretions has been associated with an increased risk of preterm delivery (Lockwood, et al., 1991). Fetal fibronectin is a large molecular weight glycoprotein found in amniotic fluid, and is thought to promote cellular adhesion at the uterine-placental and decidual-fetal membrane interfaces (Feinberg, Kliman, & Lockwood, 1991). It is released into the cervicovaginal secretions when the decidual interface is disrupted, which provides a rationale for

measurement of fetal fibronectin as a predictor or preterm delivery (Lockwood et al., 2009).

An assay to test for fetal fibronectin was developed and clinically tested between 1991 and 2000, with commercial clinical availability of a “rapid turnaround” assay in approximately the year 2000. Prior to commercial availability, the test for fetal fibronectin was used in two ways; to predict the risk of preterm delivery among women with signs and symptoms of preterm labor, and secondly to identify asymptomatic women most likely to delivery preterm.

Studies among asymptomatic women suggest fetal fibronectin is not a useful screening test for prediction of preterm delivery at less than 37 weeks gestation. The American College of Obstetricians and Gynecologists have concluded that testing should not be used routinely to screen low-risk, asymptomatic women (American College of Obstetricians and Gynecologists – ACOG, 2001).

Leitich and Kaider (2003) summarized the use of fetal fibronectin testing in symptomatic women in a systematic review of 40 prospective studies. The summary revealed approximately 80 percent of symptomatic women who went on to delivery within seven days had a positive test, however, 13 percent of symptomatic women who did not deliver within seven days also had a positive test (Leitich & Kaider, 2003). A second systematic review of studies in symptomatic women confirmed these findings and concluded that fetal fibronectin was most accurate for predicting spontaneous preterm delivery within 7 to 10 days (summary likelihood ratios for test results: positive test results

LR=5.42, 95% CI 4.36, 6.74; negative test results LR=0.25, 95% CI 0.20, 0.31) of testing (Honest, Bachmann, Gupta, Kleifnen, & Khan, 2002).

The use of fetal fibronectin testing in symptomatic women suggests the principal utility of testing lies in its high negative predictive value, which ranges from 90 to 99.5 percent (Foxman, & Petr, 2004; Giles, Bisits, Knox, Madsen & Smith, 2000; Peaceman, et al., 1997; Plaut, Smith, & Kennedy, 2003; Swamy, Simhan, Gammill, & Heine, 2005). A negative test is often used clinically to avoid unnecessary or expensive interventions such as hospital admission or glucocorticoid administration (Lockwood, et al., 2009). A cost analysis suggested the use of fetal fibronectin testing could reduce the costs of managing patients with suspected preterm labor by 50 percent (Joffe, Jacques, Bemis-Heys, Burton, Skram, & Shelburne, 1999). However, a subsequent study of women with preterm labor symptoms compared costs when fetal fibronectin results were and were not made available to clinicians found that knowledge of the test results did not lead to significant reduction in length of observation or rate of admissions (Grobman, Welshman, & Calhoun, 2004).

The positive predictive value of fetal fibronectin is less than 30 percent in most populations (Lockwood et al., 2009); however, this rate is higher than other available assessments including risk scoring, tocodynamometry, digital cervical examination and other biochemical markers. The false positive rate makes fetal fibronectin testing less than optimal for prediction of preterm delivery. Although no interventions have been demonstrated to be effective in prevention preterm delivery among fetal fibronectin positive women, a positive test does allow for

administration of glucocorticoids to hasten fetal lung maturity (Lockwood et al., 2009).

Evidence from the literature regarding the utility, diagnostic accuracy, cost, and effectiveness suggests fetal fibronectin may be a useful marker for the predicting spontaneous preterm birth (Berghammer, & Husslein, 1999; Chien, Khan, Ogston, & Owen, 1997; Goldenberg, et al., 2000a; Honest et al., 2002; Leitich, et al., 2003; Leitich et al., 2003). However, a recent meta-analysis of 32 trials with 5,355 overall participants (Sanchez-Ramos, Delke, Zamora, & Kaunitz, 2009), concluded the fetal fibronectin assay has limited accuracy in predicting preterm birth within seven days of sampling among symptomatic women (pooled sensitivity =76.1%, 95% CI 69.1, 81.9; pooled specificity =81.9%, 95% CI 78.9, 84.5).

Despite the limitations, fetal fibronectin testing is one of the best available predictors of preterm birth, however, the overall sensitivity, specificity, and positive predictive value depending upon the population, gestational age at collection, prevalence of preterm birth, and single versus multiple screening (Berghella, Hayes, Visintine, & Baxter, 2008).

The purpose of this investigation was to examine whether the availability of clinical fetal fibronectin testing had an impact on the gestational age at delivery, preterm delivery rate, neonatal intensive care unit admission rates, and differences in number of visits, admissions, or lengths of stay for treatment of preterm labor at a community tertiary-level hospital.

Background

A rapid screening test for the presence of fetal fibronectin became available at Sharp Mary Birch Hospital for Women, a tertiary level maternity hospital, in January 2001. The purpose of this historical cohort study was to examine whether the availability of the rapid assay for fetal fibronectin had an effect on the management, treatment or outcome of women presenting to the hospital triage assessment unit with signs and symptoms of preterm labor. The study compared the cohort of women seen for assessment of preterm labor in the six months prior to the assays availability to the cohort of women seen for assessment of preterm labor in the six months after the availability of the screening test. More specifically, the study investigated whether the assay had an impact on the gestational age at delivery, preterm delivery rate, neonatal intensive care unit admission rates, and differences in number of visits, admissions, or lengths of stay for treatment of preterm labor. The study also compared the fetal fibronectin testing sensitivity, specificity, negative and positive predictive values with previously published studies.

Specific Aims

The overall goal of this study was to examine whether the availability of a rapid assay for fetal fibronectin had an effect on the management, treatment or outcome of women with signs and symptoms of preterm labor at a tertiary level maternity hospital. The study compared the cohort of women seen in the six months prior to and six months after the assay availability.

The following primary specific aims examined whether the availability of the fetal fibronectin assay had an effect on:

Aim 1: The gestational age at delivery, and preterm delivery rate among women with signs and symptoms of preterm labor before and after the availability of the assay for fetal fibronectin.

Aim 2: Admission to the neonatal intensive care unit.

Aim 3: Utilization of hospital services, including outpatient triage visits, hospital admission, and total maternal and neonatal length of stay among women with signs and symptoms of preterm labor before and after the availability of the assay for fetal fibronectin.

A secondary aim of the study was to examine the outcome among those who had the test as compared to the baseline cohort, and as compared to those who did not have the test. In addition, the test sensitivity, specificity, positive predictive value and negative predictive for delivery within 14 days was examined and compared to previously published studies.

CHAPTER 2

LITERATURE REVIEW

Preterm Birth, Low Birth Weight, and Infant Mortality

Incidence

Preterm birth, or birth before 37 weeks' gestation, is a leading cause of neonatal mortality and birth-related morbidity (Martin, Hamilton, Ventura, Menacker, & Munsun 2003; Martin, et al., 2005; Martin, et al., 2008). Although the United States has one of the most advanced medical systems in the developed world, the preterm birth rate in the United States remains higher than in many other westernized countries (Holzman & Paneth, 2002; MacDormand & Mathews, 2009). The infant mortality rate of the United States ranks 30th among industrialized countries (McDormand & Mathews, 2009). Since 1999, prematurity/low birth weight has been the leading cause of neonatal mortality in the United States. Although the terms are often used interchangeably, preterm birth refers to a birth prior to 37 completed weeks' gestation, regardless of birth weight, and low birth weight (LBW) refers to birth weight less than 2,500 grams, regardless of gestational age. In 2003, 12.3% of all births were preterm (Hamilton, Martin, & Sutton 2004). This rate increased to 12.5 percent between 2003 and 2004 (Hamilton, Martin, Venture, Sutton, & Menacker, 2005), and to 12.7 in California in 2007 (Centers for Disease Control, National Center for Health Statistics, [CDC-NCHS], 2007). California's preterm birth rate is increasing despite the Healthy People 2010 objective to reduce preterm births to

a rate of 7.6 per 100 live births (California Department of Health Services [CDHS], 2005). In 2003, there were 52,881 preterm births in California, representing 10.5 percent of live births and (Peristats, 2005) higher than the 9.9 percent reported in 2001 (CDHS, 2005). In 2004, the preterm birth rate for San Diego County was 11.0 percent (CDHS, 2005). The rise in preterm births is in direct contrast to the drop in infant mortality. With considerable advances in neonatal care, the United States infant mortality rate has decreased from 26.0 per 1,000 births in 1960 (CDC, Office of Minority Health [OMH], 2004) to 6.9 deaths per 1,000 births in the United States in 2003 (United States Department of Health and Human Services [USDHHS], 2006). Despite decades of research, the etiology of preterm birth, methods to identify women at risk, and effective interventions for preterm birth prevention remain major public health and research challenges in clinical obstetrics.

Public Health Impact

Efforts to prevent preterm birth have primarily been directed toward secondary and tertiary prevention measures with only limited success in primary prevention efforts. Secondary prevention efforts have included the regionalization of perinatal care and utilization of maternal transports to specialized facilities prior to delivery, use of antenatal tocolytic medications in attempts to prolong gestation, and administration of antenatal steroids to hasten neonatal lung maturity (Haas, et al., 2005; Hohlagschwandtner, et al., 2001; Jobe & Soll, 2004; Peaceman, Bajaj, Kumar, & Grobman, 2005). Tertiary prevention has included improvements in neonatal intensive care with use of neonatal

surfactant treatments and improved ventilator management (Ainsworth, 2005; Crowther, & Harding, 2006; Peaceman et al., 2005). As a result of these prevention efforts, age specific infant mortality rates have decreased. Unfortunately, surviving infants are at an increased risk of developmental disabilities. Extremely preterm infants, born prior to 26 weeks gestation, have a high prevalence of developmental delay at 12 months (Lando, Klamer, Jonsbo, Weiss, & Greisen, 2005) and neurological and cognitive impairment when evaluated at five years of age (Marlow, Wolke, Bracewell, & Samara, 2005).

Various approaches have been used to attempt to identify women at increased risk for preterm delivery, including risk assessments, home uterine activity monitoring, serial cervical examinations, and sonographic measurements of cervical length. Identification of women at risk for preterm birth is only efficacious if preventive treatments are available. Most interventions designed to prevent preterm birth including home uterine activity monitoring, frequent health care provider contact, and administration of tocolytic medications have demonstrated limited efficacy, and many well-designed clinical trials have failed to demonstrate any reduction in preterm birth (Brown, et al., 1999; Collaborative Home Uterine Monitoring Group [CHUMS], 1995a, 1995b; Dyson, et al., 1998; Goldenberg, et al., 1998).

Preterm births have increased among singleton and multiple deliveries. Researchers have hypothesized that the increase in preterm birth rates may be attributable to the increase in multiple births from assisted reproductive technologies (Behrman & Butler, 2007). However, preterm births have increased

among singleton deliveries (Martin et al., 2003). In 2002, 10.4 percent of U.S. singleton births were preterm, compared with 60.1 percent of U.S. multiple preterm births (PeriStats, 2005). The preterm singleton and multiple California birth rates in 2003 were 8.9% and 56.5% respectively (PeriStats, 2005). The rate of multiple births increased 25% from 1996 to 2003 from 2.4% to 3.0% of all live births (PeriStats 2005).

Helmerhorst and colleagues (Helmerhorst, Perquin, Conker, & Keirse, 2004) found an increased risk of preterm birth among singletons from assisted conception (RR=2.04; 95% CI 1.80, 2.32). Advanced maternal age may also contribute as advanced maternal age deliveries (deliveries after 35 years of age) increased by 53% during the 1990s (Fiore, 2003). In 1970, the mean maternal age at first birth was 21.4 year of age, and in 2000, it was 25 years of age. The mean maternal age for all births has increased from 24.6 to 27.2 during the past 30 years (Fiore, 2003). Other potential factors that may be contributing to increased preterm births are: increases in labor induction rates (Kuehn, 2010), illicit substance abuse (Mattison, Damus, Fiore, Petrini, & Alter, 2001), or some other not yet identified factor.

Racial/Ethnic Disparities

There are persistent disparities in preterm birth rates among various racial and ethnic groups in the United States. African Americans have a disproportionately higher rate of preterm birth with a reported rate of 17.7 percent in 2002 (Martin et al., 2003). Healthy People 2010 goals include an objective to eliminate racial and ethnic disparities in all aspects of perinatal health, including

preterm birth. In California from 2001 to 2003, preterm birth rates were highest for African American infants (15.1%). Slightly elevated rates are seen for Native Americans (11.9%) when compared to whites (10%). Asians have the lowest preterm birth rate, affecting only 9.7% of all births (PeriStats, 2005).

In a review of preterm birth rates and trends in the United States from 1989 to 1997, Demissie and colleagues reported increasing preterm birth rates among whites (from 8.8% to 10.2%) and decreasing rates among African Americans during the eight year study interval (from 19.0% to 17.5%). Although the preterm birth rate among African American infants decreased from 1989 to 1997 by 7.6%, neonatal mortality only decreased by 24% as compared with a decrease of 34% among whites (Demissie, et al., 2001). The racial disparities remain poorly understood, and may be attributable to limited access to neonatal care or specific interventions (e.g., antenatal steroids or surfactant treatments), socioeconomic factors, or other unknown medical conditions or risk factors. Bacterial vaginosis, an alteration of normal vaginal flora, has been found to be independently associated with preterm delivery, and is found more frequently among African-American women than in white women (American College of Obstetricians and Gynecologists [ACOG], Practice Bulletin, October 2001).

Economic Impact

Preterm delivery may have significant economic impact on families as well as on health care systems. The annual societal economic burden associated with preterm birth in the U.S. in 2005 was $26.2 billion, or approximately $51,600 per infant born preterm (Behrman & Butler, 2007). Schmitt and colleagues

showed that infants with birth weights of 1,500 to 2,500 grams had total projected costs of $2.6 billion nationally (Schmitt S. K., Sneed L., & Phibbs C. S., 2006). In a retrospective cohort study comparing 1,683 preterm infants born at 34 to 36 weeks' gestation and 33,745 term infants in 2004, the "late-preterm" infants had an average length of stay of 8.8 days and average cost of $26,054 as compared to $2,061 for 2.2 days length of stay for term infants (McLaurin, Jall, Jackson, Owens, & Mahadevia, 2009). The total first year costs after discharge were three times higher among preterm infants as compared with term infants, and preterm infants were rehospitalized more often than term infants (McLaurin, et al. 2009). The very smallest infants comprise a disproportionate share of hospital costs. A review of California link birth cohort data for 518,704 births revealed low birth weight (LBW < 2000 grams) infants accounted for 5.9% of cases and 56.6% of hospital costs, and very low birth weight (VLBW <1500 grams) infants accounted for 0.9% of cases and 37.7% of hospital costs (Schmitt et al., 2006).

Preterm Labor Definition, Identification and Treatment

Preterm labor is defined as cervical change or effacement and uterine contractions. In 1997, the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) proposed the following criteria for more specific diagnosis of preterm labor: contractions of four in twenty minutes or eight in sixty minutes plus progressive cervical change, cervical dilation greater than one centimeter, or cervical effacement of 80 percent or greater (AAP & ACOG, 1997).

Patients with signs and symptoms of preterm labor present a diagnostic and clinical dilemma. Patients presenting with regular contractions and cervical dilation > 3 centimeters are easily diagnosed with preterm labor, however, most often therapy is not successful because labor has already progressed too far (Garite, & Lockwood, 1996). Patients not meeting the “classic” definition of preterm labor present greater challenges. For patients having no cervical dilation or effacement or less advanced cervical dilation (less than 3 centimeters), with irregular contraction activity, the diagnosis of preterm labor and treatment options are more uncertain. Even when patients meet diagnostic criteria for “preterm labor”, medications and other interventions to prevent or inhibit labor progression have not been very effective. Bed rest is one treatment historically recommended; however, a Cochrane Database System Review (Sosa, Althabe, Belizan, & Bergel, 2004) found no conclusive evidence to support or refute that bed rest is successful in prevention or treatment of preterm labor at home or in the hospital. Although approved in 1985 by the United States Food and Drug Administration, ambulatory uterine activity monitoring has not been shown to be effective in reducing the rates of preterm delivery (CHUMS, 1995a, 1995b, Dyson, et al., 1998).

The only medication approved for use by the United States Food and Drug Administration for preterm labor is ritodrine, a beta-adrenergic receptor agonist. A clinical trial of ritodrine by Leveno and colleagues (Leveno, et al., 1986) demonstrated a 24-hour delay of delivery in women treated with ritodrine as compared to no tocolytic treatment. A multi-center study of ritodrine in 1992 for

treatment of preterm labor found no significant beneficial effect on perinatal mortality, or prolongation of pregnancy to term (Canadian Preterm Labor Investigators Group, 1992). Ritodrine and other beta agonist medications may have serious and sometimes fatal side effects, including pulmonary edema, disturbance of cardiac rhythm, and myocardial ischemia (Cunningham, et al., 2001). Due to complications, ritodrine was withdrawn from the market in 2003, and it is no longer available in the United States (Cunningham, et al., 2001). Although not approved by the United States Food and Drug Administration for treatment of preterm labor, terbutaline, another beta agonist, is frequently used to treat preterm labor symptoms. Similar to ritodrine, terbutaline has been effective in temporarily arresting preterm labor, but has not reduced the rate of preterm birth rate (Goldenberg, 2002).

In addition to beta agonists, other medications used to treat preterm labor symptoms include calcium channel blockers (nifedipine), magnesium sulfate, and prostaglandin inhibitors (indomethacin). Results of clinical trials comparing the effectiveness of these medications in prevention or treatment of preterm labor have been inconclusive, and the risks and benefits remain unclear. In a review and meta-analysis of 256 publications examining tocolytic management of preterm labor, Berkman and colleagues (Berkman, et al., 2003) concluded that management of contractions with first-line tocolytic medications minimally prolonged gestation, but failed to demonstrate beneficial effect on neonatal morbidity or mortality. The authors concluded that tocolytic maintenance therapy was of little or no value (Berkman et al., 2003). There is potential for significant

adverse events associated with tocolytic use, with pulmonary edema being the most significant (Cunningham et al., 2001). Given the limited efficacy of available interventions for women identified as at risk for preterm delivery, and the potential adverse side effects of treatment, identification of patients who are not at risk for imminent preterm delivery may minimize exposure to potentially harmful medications and or interventions.

Administration of corticosteroids to hasten fetal lung maturity is among the few interventions, when used after identification of imminent preterm delivery, to improve neonatal morbidity (Crowley, 2006). Tocolytic medications may prolong gestation for a short time allowing administration of corticosteroid medications to the mother to hasten fetal lung maturity. In a meta-analysis of 15 prospective, randomized trials for the Cochrane Database System, Crowley confirmed that administration of antenatal corticosteroids significantly reduced the incidence and severity of neonatal respiratory distress syndrome. In addition, he found reduced neonatal morbidity and decreased intraventricular hemorrhage and necrotizing enterocolitis in the neonate (Crowley, 2006). However, research is needed to elucidate the optimal type of steroid medication and the number of doses necessary for reduced morbidity and mortality (Brownfoot, Crowther, & Middleton, 2008).

Although current preventive strategies and treatments for preterm labor are limited, recent studies have suggested that administration of progesterone may help to prevent preterm delivery, especially among women with a history of preterm delivery or spontaneous abortion (daFonseca, Bittar, Carvalho, &

Zugaib, 2003, Meis, et al., 2003, Rode, Langhoff-Roos, et al., 2009). Women with short cervix or preterm labor could also potentially benefit from progesterone (Rode, et al., 2009, O'Brien, et al., 2009). It is unclear whether the prolonged gestation will translate into improved maternal or long-term fetal outcomes, and side effects information associated with progesterone use is limited (Dodd, Flenady, Cincotta, & Crowther, 2006; O'Brien, et al., 2009; Rode, et al., 2009).

Pathways and mechanisms for preterm labor and preterm premature rupture of membranes.

Lockwood and Kuczynski (1999) proposed four broad pathologic pathways within the maternal-fetal environment, which could lead to activation and initiation of labor or rupture of membranes. These pathways are not mutually exclusive. The first pathway involves maternal and fetal stress with activation of the maternal or fetal hypothalmic-pituitary-adrenal-axis. The second proposed pathway involves decidual, chorioamniontic, or systemic inflammation. The third pathway is decidual hemorrhage, and the fourth pathologic uterine distention (Lockwood & Kuczynski, 1999). Maternal or fetal stress may lead to increased levels of estrogen and increased corticotropin-releasing hormone (Iams & Creasy, 2004). Excess uterine distention may occur with multiple gestations, excess amniotic fluid (hydramnios), or when uterine abnormality inhibits uterine expansion (Iams & Creasy, 2004). Increased understanding regarding the role of decidual bleeding and the uterotonic effect of thrombin has been recently described (Boggess, Moss, Murtha, Ofenbacher, & Beck, 2006; Elovitz, Baron, & Phillippe, 2001). Infection accounts for approximately 20% to

40% of spontaneous preterm births as measured by markers such as cultures or histology (Iams & Creasy, 2004). However, results of screening studies to identify and treat infections have had conflicting results. Several small studies found screening and treating women with antibiotics for bacterial vaginosis, a change in vaginal flora, reduced the risk of preterm birth (Morales, Schorr, & Albritton, 1994; Ugwumadu, Reid, Hay, Manyonda, & Jeffery, 2006). Other studies have failed to confirm these findings (Carey, Kelbanoff, & Hauth, 2000; Joesoef, et al., 1995). Antibiotic treatment for women with preterm labor has also provided mixed results. A meta-analysis of 11 randomized trials with 7428 women with preterm labor and intact membranes, found no benefit in neonatal outcome with maternal prophylactic antibiotic administration. A trend toward an increase in neonatal deaths in the antibiotic group was identified, which raises concerns about prophylactic antibiotic use (King & Flenady, 2002). Berkman, et al. (2000) found antibiotic administration only increased length of pregnancy by about 6 days (Berkman et al., 2000). Although the efficacy of prophylactic antibiotics in preterm labor remains unclear, antibiotics administered for specific documented infections is less controversial. It is recommended that women colonized with group B streptococcal disease be treated with prophylactic antibiotics intrapartum to prevent group B streptococcal neonatal sepsis (CDC MMWR, 2002), and women with asymptomatic bacteriuria during pregnancy should be treated with antibiotics to decrease the incidence of pyelonephritis and preterm birth (Smaill & Vazquez, 2007). A better understanding regarding the true relation between infection and preterm birth has been enhanced by studies

of fetal fibronectin as a potential marker for infection or inflammation in the cervicovaginal secretions in the second and third trimesters (Iams & Creasy, 2004). Interestingly, a randomized study of antibiotic administration to patients with a positive fetal fibronectin test between 22 to 24 weeks' gestation revealed no significant difference in spontaneous preterm delivery between antibiotic and placebo treated groups (Andrews & Goldenberg 2003a, Andrews, Sibai, & Thom, 2003b). However, secondary analyses from the same study (Hendler, et al., 2007) reviewed a subset of 215 fetal fibronectin positive patients meeting criteria for bacterial vaginosis between 16 and 26 weeks. Seventy-seven of 100 patients (77%) in the antibiotics group as compared to 33 of 155 (28.7%) in the placebo group became negative for bacterial vaginosis ($p < 0.001$). The rate of spontaneous preterm delivery a less than 34 weeks was lower among those with resolution of bacterial vaginosis (zero versus 5.7%, $p = 0.01$).

Review of Fetal Fibronectin Literature

Technical Aspects of Fetal Fibronectin Collection

Prior to any other vaginal examination procedures, fetal fibronectin specimens are collected during a sterile speculum examination using a Dacron swab to obtain secretions from the poste34rior cervical fornix. Initial studies of fetal fibronectin cervicovaginal specimens were analyzed by Eliza assay at a commercial laboratory (Fetal Fibronectin Enzyme Immunoassay Adeza Biomedical), with an approximate 24 to 48 hour turnaround time (quantitative assay). Patient specimens with fetal fibronectin concentrations ≥ 50 nanograms

per milliliter were defined as “positive”. The cutoff value was established using receiver-operator characteristic curve techniques developed from several earlier studies (Lockwood et al., 1991; Morrison, et al., 1993; Iams, et al., 1995). The value was determined as reasonable among women of mixed risk, however, Lu and colleagues (Lu, Goldenberg, Cliver, Kreaden, & Andrews, 2001) suggested sequential increases in fetal fibronectin values were associated with increased risk of preterm birth. They concluded the use of a single cutoff value to define a positive value in symptomatic women should be reevaluated. Due to the prolonged turnaround time with the early assays, many women may have already “declared” their diagnosis by progressing to delivery or experiencing cessation of preterm labor symptoms, limiting the clinical usefulness of the assay. Subsequent studies used a rapid turn around TLi assay, conducted on-site in the hospital laboratory, with an approximate 1 to 3 hour turnaround time. Early studies had limited inclusion and exclusion criteria; however most studies after FDA approval of the TLi testing system (Adeza Biomedical, TLi Testing System, Sunnyvale, California 1999) used the labeling inclusion criteria for fetal fibronectin assay of singleton intrauterine pregnancy, approximately 24 to 35 weeks gestation, with intact membranes. Exclusion criteria for most studies included cervix more than 3.0 cm dilated or current vaginal bleeding. Additional exclusion criteria were sexual intercourse, digital examination or amniocentesis within 24 twenty-four hours of testing.

Identification of Fetal Fibronectin

Biochemical markers associated with uterine contractions and disruption of the extra cellular matrix within the cervical and fetal membranes are potential risk factors for preterm delivery. An isoform of fibronectin found exclusively in malignant tumors and in fetal tissues, including the placenta and amniotic fluid, was identified and described by Matsuura and Halomori in 1985, and subsequently recognized by the monoclonal antibody FDC-6 (Matsuura, et al., 1988). A potential marker for detection of inflammation and infection, fetal fibronectin has been studied extensively over the past decade.

Fetal fibronectin is normally found in the cervix during early pregnancy. After approximately 20 weeks' gestation, the cervix is fibronectin-free until labor begins (Iams & Creasy, 2004). It appears that fetal fibronectin plays a role in the extracellular interface, perhaps as an adhesion protein connecting the placenta and the uterus (Koenn, 2002). It may also be important in cleavage of the placenta following delivery (Garite & Lockwood, 1996). A glycoprotein in the interface between the chorion and decidua, fetal fibronectin may be found on the cervix and in the vagina when this interface is unstable (Lockwood et al., 1991). When the extracellular matrix is broken down because of stress, hemorrhage or infection, fetal fibronectin is able to "leak" into the cervicovaginal secretions (Lockwood et al., 1991; Lockwood, et al., 1993; Weismiller, 1999) and this may serve as a logical marker for preterm labor.

Review of clinical studies

Key clinical studies were reviewed, summarized, and presented in tabular format in Appendix A, Table 7. Lockwood and colleagues (1991) first hypothesized the presence of fetal fibronectin in vaginal secretions as a potential marker for impending preterm labor. In a multicenter study, 163 pregnant women with either preterm premature rupture of membranes (n=65) or preterm contractions with intact membranes (n=117) were compared to 163 normal asymptomatic pregnancy controls. Among the patients with contractions and intact membranes, women with cervical or vaginal fibronectin were more likely to deliver preterm as compared with women without fetal fibronectin present (83.1% vs. 19.0%, $p<0.01$). The presence of fetal fibronectin had a sensitivity of 81.7% and specificity of 82.5% in identification of deliveries before 37 weeks (n=60). Results suggested the presence of fetal fibronectin in cervicovaginal secretions during the second and third trimesters of pregnancy identified women at increased risk for preterm delivery.

Early clinical studies evaluated fetal fibronectin as a potential screening test to identify women at risk of preterm delivery. Nageotte and colleagues (Nageotte, Casal, & Senyei, 1994) evaluated weekly fetal fibronectin specimens among 87 asymptomatic women with historical risk factors for preterm delivery and found the fetal fibronectin test had a sensitivity of 92.6%, specificity of 51.7%, positive predictive value of 46.3%, with any positive test at sampling considered a positive result (Nageotte et al., 1994). Among the most significant findings, of the 33 patients who never had a positive test, only two delivered

prematurely, with a 93.9% negative predictive value (Nageotte et al., 1994). In addition, sampling every 2 or 3 weeks was as effective as weekly sampling (Nageotte et al., 1994). In another study of asymptomatic, low-risk patients, 429 patients were screened every two weeks between 24 and 35 weeks gestation (Lockwood et al., 1993). Results of the study identified a sensitivity of 67 percent with any positive test and negative predictive value of 94% if all tests were negative (Lockwood et al., 1993).

The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network conducted a large screening study of fetal fibronectin for preterm birth among asymptomatic women in a relatively low-risk population at less than 28 weeks' gestation (Goldenberg, et al., 1996a). Among 2,929 women screened every two weeks for cervical and vaginal fetal fibronectin between 22 - 24 weeks through 30 weeks' gestation, a positive test predicted more than half of the spontaneous preterm births at less than 28 weeks' gestation (sensitivity 63%).

Bartiniki and colleagues (Bartinicki, Casal, Kreaden, Saling, & Vetter, 1996) analyzed vaginal secretions for the presence of fetal fibronectin among 112 patients with symptoms of preterm labor between 22 and 35 weeks and observed a sensitivity, specificity, positive and negative predictive values of 67.5%, 90.3%, 79.4%, and 83.3% respectively, for prediction of preterm delivery. Peaceman and colleagues (1997) collected fetal fibronectin specimens from 763 symptomatic women with symptoms of preterm labor between 24 and 35 weeks and found a negative predictive value of 99.5% for delivery within 7 days. Lukes

and colleagues analyzed 763 patients with symptoms between 24 and 35 weeks, and the simultaneous effects of multiple variables on predicting positive fetal fibronectin results, and concluded the most significant to predict positive results included cervical dilation, sexual activity or cervical manipulation within 24 hours of sample collection, vaginal bleeding and uterine contractions (Lukes, Thorp, Eucker, & Pahel-Short, 1997). Subsequent studies began excluding patients with advanced cervical dilation, cervical manipulation or sexual activity within 24 hours, or bleeding in an attempt to decrease the number of false positive results.

In 1997, Chien and colleagues reviewed fetal fibronectin studies conducted from 1966 to 1996 and summarized 723 symptomatic women from nine studies and 847 asymptomatic women (635 low risk, 212 high risk) from six studies. The authors developed likelihood ratios for positive and negative tests using the outcomes of delivery < 37 weeks, delivery < 34 weeks, and delivery within one week. The authors concluded that the test provided only minimal prediction of delivery at < 37 and <34 weeks gestation above the baseline prevalence rates in symptomatic and asymptomatic women, however, a moderate improvement in the probability of preterm delivery within one week of testing. In symptomatic women with a pretest probability for positive results of 6.6, posttest probability was 25.8 (LR positive result =5.0, 95% CI 3.8, 6.4). The pretest probability for negative results was 6.6 and posttest probability was 1.2. (LR negative result =0.2, 95% CI 0.1, 0.4). The authors concluded the most appropriate measure of outcome in symptomatic women is delivery within one week; however only four of the studies reviewed reported this outcome measure

(Chien et al., 1997). The lack of homogeneity among the various early studies limited pooling of results, especially with significant variability in reported sensitivity and specificity values. A subsequent meta-analysis conducted by Leitich and colleagues in 1999 pooled estimates for sensitivity and specificity among 27 studies with 3185 and 2812 patients for delivery at <37 weeks and <34 weeks respectively, and concluded that the test most effectively predicted birth within 7 days of sampling among symptomatic patients with a sensitivity of 89% (95% CI 80, 97) and specificity of 86% (95% CI 81, 91) (Leitich et al., 1999).

Joffe and colleagues conducted a “before assay” and “after assay availability” historical cohort study in 1999. Despite the 24 to 48 hour reporting time required for the quantitative assay results, the study demonstrated a significant decrease in admissions for preterm labor, decreased length of stay for admitted patients, and decreased use of tocolytic medications after the availability of the assay. They did not, however, demonstrate an impact on neonatal outcomes (Joffe et al., 1999).

Subsequent studies examined the rapid turnaround assay to determine which patients with signs and symptoms of preterm labor require clinical treatment with tocolytic medications, admission to the hospital, or transfer to a tertiary level center. Giles and colleagues found a negative fetal fibronectin result decreased maternal transports for treatment of preterm labor by 90% and reduced the use of tocolytics by 64% (Giles, Bisits, Knox, Madsen, & Smith, 2000). Sullivan and colleagues (2001) performed cost-analysis modeling in a retrospective review of an 11 month interval of symptomatic preterm labor

patients, and concluded the fetal fibronectin assay may be cost effective in reducing admission and costs if used only after a clinical decision on hospital admission is made (Sullivan, Hueppchen, & Satin, 2001).

The largest study of fetal fibronectin as a second trimester predictor of preterm labor was the Preterm Prediction Study (Goldenberg et al., 1996a; Goldenberg, et al., 1996b; Goldenberg, et al., 2001; Lu, Goldenberg, Cliver, Kreaden, & Andrews, 2001). Using serial fetal fibronectin specimen collection from asymptomatic patients between 24 and 35 weeks, a patient with a positive fetal fibronectin test at 22 to 24 weeks gestation had a 14 times greater chance of delivering a baby at less than 32 weeks. This and other studies have demonstrated that a positive fetal fibronectin test in the second trimester is also associated with a higher risk of bacterial vaginosis, preterm premature rupture of membranes, and shortened cervix of <2.5 centimeters (Goldenberg et al., 1996; Goldenberg et al., 2001; Stevens, et al., 2004). Goldenberg and colleagues also demonstrated these risk factors may have an exponential effect on the risk of preterm birth. The presence of any two of these risk factors would suggest a 35 times increase in the likelihood of preterm birth, and all three factors would suggest a 100 times increase in the risk of preterm birth (Goldenberg et al.; Goldenberg et al.,1996a; Goldenberg et al.,1996b; Goldenberg et al., 2001).

Rinehart and colleagues (Rinehart, et al., 2001) conducted a prospective cohort examination among 235 women with signs and symptoms of preterm labor between 24 and 34 weeks gestation, without cervical change, which is typically required to meet the “classic” definition of preterm labor. The authors

reported a prevalence of 20 percent positive fetal fibronectin assays. The most significant finding from this study was high negative predictive value for delivery within 7 days (94%) and less than 28 weeks (100%), providing evidence to support the conclusion that among patients with symptoms without cervical change, patients with a negative fetal fibronectin are less likely to delivery with 7 days or at less than 28 weeks.

Plaut and colleagues (Plaut et al., 2003) conducted a prospective, randomized study on 108 patients with symptoms of preterm labor between 24 and 35 and randomized the patients to two groups; results of fetal fibronectin results known to care providers versus results unknown. They found hospital stay was not significantly shorter for negative results between the known and unknown groups. Foxman and colleagues (Foxman et al., 2004) used a physician survey at the time of test requisition among symptomatic patients between 24 and 34 weeks and concluded that the availability of the fetal fibronectin assay reduced hospital stay for admissions for preterm labor. However, the study utilized a “survey” design with presumptive diagnosis by the physician at the time of test request to ascertain whether admission was planned, as opposed to a more rigorous study design using randomized comparison of groups. Grobman and colleagues (Grobman et al., 2004) conducted a randomized comparison of results known versus results unknown to examine the assay effect or outcomes in 100 symptomatic patients between 24 and 34 weeks and found no significant differences in hospital admissions, tocolysis, work cessation, or total costs.

Lowe and colleagues (Lowe, Zimmerman, & Hansen, 2004) examined whether fetal fibronectin had an effect on length of stay and preterm labor interventions by randomizing patients to fetal fibronectin versus no fetal fibronectin. Among 97 symptomatic patients between 23 and 34 weeks gestation with physicians unblinded to study results, a negative fetal fibronectin was associated with fewer admissions ($p=0.032$) and decreased length of stay ($p=0.008$).

Abenhaim and colleagues (Abenhaim, Morin, & Benjamin, 2005) conducted a study in Canada to examine whether the availability of the fetal fibronectin assay affected utilization of hospital resources. The authors used a comparison of a 20 week historical cohort (n=116) versus 20 week prospective cohort (n=116) to examine symptomatic patients between 24 and 34 weeks and found decreased admissions after the availability of the assay (24.1% versus 12.1%, $p=0.03$). They found decreased mean length of stay after the availability of the assay (5.2 versus 0.6 days, $p<0.0001$) but did not find a significant difference in preterm delivery prior to 37 weeks between the two cohorts (Abenhaim et al., 2005).

Gomez and colleagues (Gomez, et. al., 2005) from Chile, combined the fetal fibronectin assay with cervical length to examine whether the combined tests would improve diagnostic capability. The prospective cohort study of 215 symptomatic patients between 22 and 35 weeks, found both tests performed comparably in the prediction of preterm delivery ($p<0.01$ for each). A significant improvement in the prediction of preterm delivery was achieved when combining

fetal fibronectin results with cervical length, but only if the cervical length was less than 30 millimeters (Gomez et al., 2005).

Musaad and colleagues in Austrialia (Musaad, Melson, & Boswell, 2005) conducted a study using a historical cohort comparison (n=30) with a prospective cohort (n=30) to examine management costs, hospital costs and length of stay after the availability of the rapid assay and found no significant differences before and after the availability of the assay. However the study was limited by small sample size, using only the first 30 fetal fibronectin tests conducted, the timeframe was not given, and cases were matched with controls from previous nine months.

Tekesin and colleagues in Germany conducted two prospective cohort studies (Tekesin, Marek, Hellmeyer, Reitz, & Schmidt, 2005a; Tekesin, Wallweiner, & Schmidt, 2005b) to examine use of fetal fibronectin in symptomatic patients between 24 and 34 weeks. In a study of 117 patients, the authors evaluated clinical risk factors, fetal fibronectin, and cervical characteristics (“gray area” to quantify cervical mass) and determined the combining the tests improves diagnostic efficiency, especially with a “low gray” determination for cervical mass combined with a positive fetal fibronectin assay (RR=24.8). The second prospective cohort study examined 170 symptomatic patients between 24 and 34 weeks and found a decreased mean gestational age at delivery among women with a positive fetal fibronectin assay versus patients with a negative fetal fibronectin assay (35.71 versus 38.63, $p<0.001$), and decreased time from admission to delivery (36.1 versus 63.4 days, $p<0.001$). In addition,

the negative predictive value for delivery in less than 7 and less than 14 days was 98.4%.

Swamy and colleagues examined whether fetal fibronectin could be used in the clinical setting to guide clinical management (Swamy, Simhan, Gammill, & Heine, 2005) by implementing a clinical pathway to be used at the discretion of the practitioner. The patients were divided by fetal fibronectin result and compared (n=46 positive versus n=358 negative) to predict the outcomes of delivery within 7 and 14 days and prior to 32 or 37 weeks. For delivery within 7 days of fetal fibronectin sampling, the negative predictive value was consistent with other studies (NPV =98%). A positive test was predictive of birth within 7 days (RR=22.0) and time until delivery (days) using Kaplan-Meier curves. The Wilcoxon log rank test was used to demonstrate a significant difference between the two curves ($p<0.05$).

Most recently, Tsoi and colleagues in London and South Africa (Tsoi, Akmal, Geerts, Jeffery, & Nicolaides, 2006) combined cervical length and fetal fibronectin in symptomatic patients (n=195) between 24 and 34 weeks with physicians blinded to the fetal fibronectin results. The authors found a significant association between cervical length and positive fetal fibronectin ($p =0.003$). Using logistic regression to predict delivery within 7 days, the only positive predictor was cervical length in a model that included fetal fibronectin, ethnicity, maternal age, gestational age, body mass index, parity, history of prior preterm delivery, cigarette smoking and tocolysis. The authors concluded that

assessment of fetal fibronectin did not improve the prediction of preterm delivery within 7 days provided by the cervical length measurement.

Since the discovery of the link between the presence of fetal fibronectin and subsequent preterm delivery by Lockwood and colleagues in 1991, there have been over 120 publications (Lockwood, Ramin, & Varss, 2009) and according to the manufacturer, over 40,000 tests were performed each month in 2008 (Lockwood, et al., 2009). The principal utility of fetal fibronectin testing lies in the high negative predictive value for delivery within 7 to 14 days. In a review cited by ACOG, 99.5% of symptomatic women with a negative fetal fibronectin test failed to deliver within 7 days, and 99.2% remained undelivered for 14 days (ACOG 2001). A cost analysis study suggested the clinical use of a negative test to avoid hospital admissions and unnecessary or expensive interventions may reduce the costs of managing patients with preterm labor by 50 percent (Joffe, et al., 1999). However, knowledge of fetal fibronectin result did not lead to significant reductions in length of initial hospital observation, hospital admission, or tocolysis or total health care related costs (Grobman et al., 2004), which has been interpreted to suggest that perhaps fetal fibronectin is cost effective only when clinicians are comfortable using the results to alter patient care (Lockwood, et al., 2009).

The high false positive rate makes it less optimal for predicting preterm delivery, however, the principal utility of fetal fibronectin testing lies in the high negative predictive value, which is usually greater than 99% (Lockwood, et al., 2009). A negative fetal fibronectin test may provide reassurance to a woman

with signs and symptoms of preterm labor. A negative test also provides evidence for her health care provider that she is unlikely to deliver within the next 7 to 14 days, which may lead to decreased interventions and admissions.

Preterm Birth and Risk Factors

Preterm birth is considered “multifactorial” as it may be preceded by numerous and diverse maternal and pregnancy associated risk factors. Preterm labor, preterm rupture of membranes, multiple gestation, preeclampsia, abruption of the placenta, placenta previa, polyhydramnios or oligohydramnios, anomalies, amnionitis, incompetent cervix, and maternal medical conditions including diabetes, connective tissue diseases, and hypertension may each lead to preterm delivery (Iams & Creasy, 2004; Iams, et al., 1998; Goldenberg et al.,1998; Goldenberg, et al., 2003; Meis, et al., 1997). Other potential risk factors associated with preterm delivery include ethnicity, history of previous preterm delivery, periodontal disease, low prepregnancy weight, maternal age less than 18 or greater than 35 years, strenuous work, high stress, anemia, cigarette smoking, bacteriuria, genital colonization or infection, cervical abnormalities or surgeries, uterine abnormalities and uterine irritability (Iams & Creasy, 2004; Iams et al., 1998; Goldenberg et al., 1998; Goldenberg et al., 2003; Meis et al., 1997). Meis and colleagues (Meis, et al., 1998) categorized the conditions and risk factors associated with preterm delivery into two broad categories, indicated and spontaneous preterm deliveries. Indicated preterm deliveries include medical or obstetric disorders placing the mother or fetus at risk such as maternal hypertension, preeclampsia, diabetes, placenta previa, placental

abruption or fetal growth restriction. These deliveries account for approximately 25 percent of preterm births (Iams & Creasy, 2004). The remaining 75 percent are considered spontaneous preterm births, and are typically a result of preterm labor, preterm ruptured membranes, incompetent cervix or amnionitis (Iams & Creasy, 2004). Approximately 80 percent of the spontaneous preterm births are thought to be the result of uterine contractions (preterm labor) or preterm premature rupture of membranes (Mattison et al., 2001).

Specific Risk Factors

The three risk factors cited most frequently as associated with preterm birth include history of preterm delivery (ACOG 2001), current multifetal pregnancy (Martin et al., 2003), and certain uterine and/or cervical anomalies (March of Dimes, 2004). A woman with a history of prior preterm birth has a threefold increase of recurrent preterm delivery as compared with women whose first delivery was not preterm (Bloom, Yost, & Mcintire, 2001). Multiple pregnancies are known to have shortened gestation. In 2001, 57 percent of twins and 92 percent of triplets were born before 37 weeks' gestation (Iams & Creasy, 2004). Preterm birth is higher among women with uterine and/or cervical malformations potentially from abnormal placentation, lack of uterine distensibility, or abnormal cervical function. A specific example is the t-shaped uterus that may be present among women exposed in utero to diethylstilbestrol (Iams & Creasy, 2004).

Other possible risk factors include medical conditions such as infection, especially genito-urinary infections (ACOG 2001; Goldenberg 2002; Klein &

Gibbs, 2005). Potentially 50% of spontaneous preterm births may be associated with infection (Klein & Gibbs, 2005). Intrauterine infection may activate the maternal and fetal inflammatory pathway and lead to uterine contractions or preterm premature rupture of membranes. A number of studies have suggested that abnormal vaginal flora, as with bacterial vaginosis, may increase risk of preterm delivery, however treatment with antibiotics has not been demonstrated to consistently reduce the rate of preterm delivery. An increase in preterm births among women treated for bacterial vaginosis with antibiotics has been reported in several clinical trials (Andrews & Goldenberg, 2003a; Andrews, Sabai, & Thom, 2003b; Carey et al., 2000; Klebanoff, Carey, & Hauth, 2001,).

Diabetes mellitus and pregnancy hyperglycemia were associated with risk of spontaneous preterm birth in a cohort study of 46,230 pregnancies conducted by Hedderson and colleagues in 2003 (Hedderson, Ferrara, & Sacks, 2003). The risk of preterm birth was increased with increasing levels of glycemia, and the association was independent of other perinatal complications that could have triggered preterm delivery (Hedderson et al., 2003).

Maternal age younger than 17 and older than 35 years have historically been identified as risk factors for preterm birth (ACOG 2001). Cleary-Goldman and colleagues analyzed a prospective database of 36,056 singleton pregnancies and found increasing maternal age was independently associated with adverse pregnancy outcomes, and that women aged 40 or older had a 40% increased risk of preterm delivery (Cleary-Goldman, et al., 2005). Review of the literature consistently identifies a relationship between older maternal age and

preterm birth. However, there is insufficient evidence to determine if older maternal age is an independent and direct risk factor for preterm birth and small for gestational age birth, or a risk marker that exerts its influence through association with age-dependent confounders (Newburn-Cook & Onyskiw, 2005).

Clinical Identification and Interventions for Women at Risk

Half of all preterm births occur in women without identifiable clinical risk factors (Iams & Creasy, 2004). Identification of risk factors fails to identify up to 70% of patients who will deliver preterm (Kurtzman 2009). Risk scoring systems have been proposed to identify women at greatest risk for preterm birth; however, these systems are unsuccessful in predicting preterm birth (Mercer, et al., 1996). The optimal test or biomarker to test for risk of preterm birth would correctly identify those who are or are not at risk. Previous research regarding fetal fibronectin suggests the high false positive rate makes it less optimal for predicting preterm delivery, however, the principal utility of fetal fibronectin testing lies in the high negative predictive value, which is usually greater than 99% (Lockwood, et al., 2009). A negative fetal fibronectin test may provide reassurance to a woman with signs and symptoms of preterm labor. A negative test also provides evidence for her health care provider that she is unlikely to deliver within the next 7 to 14 days, which may lead to decreased interventions and admissions.

The purpose of this study was to evaluate the introduction of a rapid turnaround assay for fetal fibronectin in a community-based hospital, and whether the availability of the assay would lead to decreased rates of preterm

birth, NICU admission, and utilization of hospital services. Previous studies had been conducted in controlled academic settings. This study allowed historical review and examination of whether the research findings seen in academic centers would be replicated in a community hospital setting among multiple providers with varied practice patterns in non-academic setting.

CHAPTER 3

METHODS

Specific Aims

The overall goal of this study was to examine whether the availability of a rapid assay for fetal fibronectin had an effect on the management, treatment or outcome of women with signs and symptoms of preterm labor at a tertiary level maternity hospital. The study compared the cohort of women seen in the six months prior to and six months after the assay availability.

The primary aims were to examine whether the availability of the fetal fibronectin assay had an effect on:

Aim 1: Gestational age at delivery, or preterm delivery rate among women with signs and symptoms of preterm labor.

Aim 2: Admission to the neonatal intensive care unit.

Aim 3: Utilization of hospital services, including outpatient triage visits, hospital admission, and total maternal and neonatal length of stay among women with signs and symptoms of preterm labor before and after the availability of the assay for fetal fibronectin.

A secondary aim of the study was to examine the outcomes among those who had the test as compared to the baseline cohort. In addition, the test sensitivity, specificity, positive predictive value and negative predictive for delivery within 14 days was examined and compared to previously published studies.

Study Design

The study data were obtained as part of a retrospective cohort study of women presenting with signs and symptoms of preterm labor at a community based tertiary level women's hospital with approximately 7000 deliveries per year. Medical staff at the time of the study included approximately 89 community obstetricians and 6 maternal fetal medicine specialists providing prenatal care and performing deliveries. The study was reviewed and approved by the hospital Institutional Review Board, and the Human Subjects Review Committees at the University of California at San Diego and San Diego State University. Beginning in January 2001, testing of cervicovaginal secretions for the presence of fetal fibronectin with the rapid turnaround TLI laboratory assay was available twenty-four hours per day, seven days per week, with approximately one to two hour result turnaround time.

Study Population

The study sample included women presenting to the hospital triage assessment unit in the six months prior to the availability of the fetal fibronectin test, between June 30, 2000 and December 31, 2000, and the six months after the availability of the test, between January 1, 2001 and July 1, 2001. Women with an ICD-9 code 644.03 rule-out preterm labor were identified using triage logbooks and electronic coding search. Computerized charting records and written medical records were reviewed and data retrospectively collected on all women meeting inclusion criteria for appropriate fetal fibronectin testing.

Inclusion and Exclusion Criteria

Inclusion criteria for the study were intrauterine singleton pregnancy, gestational age of 24 weeks 0 days to 34 weeks 6 days, and triage visit to hospital with signs and symptoms of preterm labor. Exclusion criteria included confirmation of ruptured membranes, cervix dilated to more than 3.0 centimeters, and vaginal bleeding. Additional exclusion criteria included sexual intercourse, digital examination, or amniocentesis in prior twenty-four hours. Patients also must have ultimately delivered at the same hospital to allow collection of outcome data. Patients with preterm deliveries for medical indications (maternal or fetal compromise) and/or primary medical diagnoses rendering them inappropriate for fetal fibronectin testing were not included in the study.

Study Procedures

Electronic and printed medical records were reviewed and data collected by two trained and experienced data collectors using a data collection form (Appendix 1). Maternal demographic and pregnancy data were collected on all eligible patients including maternal age, ethnicity, gravidity, parity, prior preterm deliveries, live births, spontaneous and therapeutic abortions, number of live births, and gestational age at time of test collection. Data regarding confirmation of test appropriateness were collected including confirmation of signs and symptoms for “rule-out preterm labor” diagnosis, cervical examination results, uterine contraction activity, bleeding, evidence of infection, and history of vaginal

examination or intercourse in prior 24 hours. Visit specific data collected included date and time of triage visit and time of test collection, gestational age at time of fetal fibronectin testing, and test results. Outcome information including gestational age at delivery was collected using best estimate for gestational age from delivery summary information.

Variables collected from maternal and newborn medical record included:

1. Maternal Variables
2. Demographic variables
    a. Maternal age
    b. Ethnicity
3. Reproductive variables
    a. Gravidity
    b. Parity
    c. Previous preterm delivery
4. Pregnancy related variables, current pregnancy
5. Hospital triage visits
    a. Gestational age at triage visit
    b. Hospital admissions
    c. Total number of triage visits for preterm labor signs and symptoms
    d. Hospital length of stay
    e. Gestational age at delivery
    f. Type of delivery
    g. Fetal fibronectin tests and results

6. Neonatal Variables
    a. Gestational age at birth
    b. Birth weight
    c. Admission to neonatal stepdown or intensive care unit
    d. Length of hospital stay

Dependent and Outcome Variables

Preterm Delivery

Gestational age at delivery was recorded from the computerized labor and delivery summary, which is completed by the physician after delivery. This information is a computer calculation and a "best estimate" from the delivering physician based upon most recent ultrasound evaluation, dates using last menses, or estimated date of confinement if no ultrasound examination was performed. Preterm delivery was dichotomized as delivery before versus after completion of 37 weeks gestation, and also further examined by categorizing gestational age at delivery to elicit more specific information related to deliveries prior to completion of 32, 35, and 36 completed weeks gestation.

The "rule-out preterm labor" coding diagnosis was based upon physician designated diagnosis and hospital ICD-9 and CPT coding for 644.03 "early or threatened labor" which is defined as "preterm labor after 22 weeks, but before 37 completed weeks of gestation without delivery" (Ingenix ICD-9-CM 2006). Diagnosis and treatment of preterm labor are "based upon inadequate literature…, and incomplete understanding of the sequence and timing of events

that precede clinical evidence of preterm labor" (Behrman & Butler, 2007). The standard criteria for diagnosis of preterm labor are "uterine contractions accompanied by cervical change" (Behrman & Butler, 2007). However, the progression of symptoms may be gradual making diagnosis imprecise. Preterm labor is typically considered clinically whenever a women presents with abdominal or pelvic symptoms like pelvic pressure, cramps, and contractions. The traditional criteria for diagnosis are reasonably accurate (persistent uterine contractions with cervical change) when contraction frequency is six or more contractions per hour (Behrman & Butler, 2007). However, due to the uncertainty of diagnosis and the increased morbidity associated with preterm labor, physicians often utilize lower thresholds for contraction frequency and symptom criteria for diagnosis, making a false-positive diagnosis of preterm labor in up to 40 percent of cases (Behrman & Butler, 2007).

Neonatal Intensive Care Admission

Data regarding admission to the neonatal intensive care unit (NICU) or stepdown intensive care data were collected from the neonatal computerized medical record. Admission to other than maternal newborn care unit was recorded as the total number of days in NICU or stepdown care and subsequently dichotomized as NICU "admitted" versus "not admitted" for analyses.

Hospital Visits and Services

Data for all antenatal triage visits and hospital admissions resulting from triage visits for signs and symptoms of preterm labor were collected from the

maternal medical record. The total number of triage visits as well the number of antenatal hospital admissions were collected in addition to a summary measure for the total number of maternal hospital days. The total maternal length of stay was a summary measure inclusive of all antenatal, intrapartum and postpartum hospital days recorded in the maternal medical record during the pregnancy.

Fetal fibronectin testing information and results were collected from the maternal medical record as well as from laboratory records and triage logbooks. The patient signs and symptoms of preterm labor were recorded as well as uterine contraction activity. Chief complaint and physical examination results were reviewed to ascertain appropriateness for diagnosis of “rule-out preterm labor” and fetal fibronectin testing inclusion and exclusion criteria. Cervical examination results were recorded as dilation and effacement in centimeters, and station was recorded on a scale of +3 to -3. Antenatal steroid administration during the time of the triage evaluation visit was recorded as “no” or “yes”. Days to delivery was calculated by subtracting the date of fetal fibronectin testing from the date of delivery, expressed as the number of days to delivery after testing, and dichotomized as delivery within 14 days “no” versus “yes” for analyses.

Gestational age at delivery was collected from the maternal delivery summary and subsequently stratified and dichotomized for analyses. Neonatal length of stay was collected as a summary measure for total days in hospital inclusive of NICU, stepdown, and maternal newborn unit care. Additional neonatal outcome measures recorded from the neonatal electronic medical record included the diagnosis of respiratory distress syndrome (“yes” versus “no”) and the actual

number of doses of surfactant, which was dichotomized to “yes” or “no” and whether ventilation was required. In addition, the gender and infant status (viable well, viable with compromise, demise) was recorded as well as a description of anomalies.

Description of Baseline, Demographic and Independent Variables

Maternal age was defined as age at the time of the qualifying triage visit. Frequency distribution and descriptive statistics and measures of central tendency for maternal age were reviewed and the data was plotted for each study period (2000 and 2001). The distribution revealed an approximately normal distribution, which allowed comparison of mean maternal age at entry to the study between the baseline (2000) and after test (2001) cohorts. Maternal age was further stratified to allow additional examination, and based upon the distribution of the data, the categories of 16-24 years, 25-34 years, and > 34 years were created.

Coding ethnicity included over 27 categories for self-reported combined ethnicity categories, which were collapsed to five major categories for analysis; Caucasian, Hispanic, African American, Asian, or other/missing/not specified. The other/missing/not specified category was not included in analyses after the baseline comparisons. Dummy variables were created for the four remaining categories and Caucasian was used as the reference category in the analyses.

Number of previous deliveries (parity) was first examined as a continuous variable, which revealed a non-normal distribution, and was subsequently

categorized using the four categories (none, 1, 2, 3 or more) and subsequently collapsed into two categories (none, one or more) due to sparse data. Number of previous preterm deliveries was first categorized into three categories (none, 1, 2 or more) and subsequently to a dichotomous variable (history of preterm labor no/yes).

Gestational age at the first triage visit as a continuous variable revealed a normally approximated distribution. The data were categorized to allow further examination using clinically intuitive ranges of 24.0 - 28.0, 28.1 - 32.0, and 32.1 - 34.6 weeks gestation.

Exploratory review of the distribution of the total number of triage visits revealed a non-normal distribution due to subjects with multiple visits and the variable was subsequently dichotomized to one and > 1 triage visit.

Maternal length of stay was collected from medical record review as a summary variable to include all antenatal, intrapartum and postnatal hospital days. Although the number of antenatal admissions was collected, the actual number of hospital days prior to delivery was not collected and not available for analysis.

Days to delivery was defined as total days from first triage visit to delivery among the patients in each cohort. Antenatal steroid administration was a dichotomous measure (no/yes). Maternal hospital admission for signs and symptoms of preterm labor based (no/yes) at time of each triage visit for each subject. The total number of admissions was summarized for each cohort.

Neonatal length of stay was intuitively categorized as 1-2 days, 3-4 days, 5-10 days, 11-30 days, and 31-61 days after review of data. Dichotomous neonatal variables (no/yes) included neonates receiving surfactant, ventilation required, intraventricular hemorrhage, respiratory distress syndrome and gender.

Fetal Fibronectin Test Variables

The number of fetal fibronectin tests for each month of the study were summarized and divided by the number of qualifying triage visits for the same month to allow a number of tests divided by visits percentage to examine test utilization rate during the six-month study interval with test availability (2001). Sensitivity, specificity, negative and positive predictive values for preterm delivery within 14 days after fetal fibronectin testing were examined using all 215 tests for 183 subjects. Summarization of descriptive characteristics for women who had fetal fibronectin testing included women having repeated testing as well as the triage visit number resulting in positive fetal fibronectin test, patients with positive test at first test, and patients having a positive test after multiple tests.

Statistical Analysis

Data were analyzed using SPSS (Version 15, SPSS Inc, Chicago, IL, U.S.A.) and Epi-Info (2002, Centers for Disease Control, Atlanta, GA, U.S.A.). Data were first verified for accurate data entry, formats, coding and missing observations. The largest and smallest values for each variable were reviewed and examined for accuracy and plausibility. Each variable was also examined for

variability, and frequency distribution, skewness and kurtosis. Data were subsequently evaluated using descriptive, univariable and adjusted analyses. Multivariable analyses were conducted related to the specific study aims. All significance tests were two-sided with a critical alpha level of 0.05. Comparison of demographic and pregnancy characteristics were made using logistic regression, Chi square or Fisher's Exact testing for dichotomous and categorical variables, t-tests for comparison of means for continuous variables, and the Mann-Whitney Wilcoxin Rank Sum test was used as a non-parametric test for ordered categorical variables or for continuous variables failing to meet normal distribution assumptions.

Univariable and age-adjusted analyses between the dependent variable and each independent variable were carried out to examine the crude associations between variables. The relationship between the dependent variable and each independent variable was examined using chi-square or Fisher's Exact testing, analysis of variance (ANOVA), Mann-Whitney Wilcoxin Rank Sum test, or logistic regression. Age-adjustment was carried out using analysis of variance or logistic regression. Repeated measures analyses were carried out using Poisson regression modeling and generalized estimating equation modeling.

Multivariable Model Building Strategy

Logistic regression analyses were performed to examine relationships among the dependent and independent variables while simultaneously

controlling for the effects of other variables in the models. The selection of variables as potential confounders was based upon published literature and empirical findings in the data. The goal was the selection of the appropriate combination of covariates to control for confounding with the most precise and efficient model. Any variable with a univariable test result with a p value< 0.25 was chosen for inclusion in the multivariable model along with other variables known to be clinically important. A significance level of 0.25 was used rather than the more traditional level of 0.05, which can fail to identify variables known to be important (Hosmer & Lemeshow, 2000). Once all potential variables were identified, the relationship with the dependent variable was assessed by comparing the estimated coefficient for the variable from models with and without the variable. Variables not included in the initial multivariable model were added back in to some models. The coefficients were then compared to ascertain change in potential relationships with the presence of new variables in the model. Variables were retained in the multivariable model if the observed change in coefficient was greater than 10% regardless of the statistical significance of the estimated coefficient.

First order interactions were tested and retained in the model if statistically significant. Regression diagnostics were performed on the logistic regression models. Residual analyses were performed to assess regression assumptions. Collinearity was assessed using correlation matrices. Goodness-of-fit was assessed using the Hosmer-Lemeshow test with the null hypothesis that the model was a good fit, and an alpha acceptance level of 0.10.

Poisson regression models and generalized estimating equations were used to adjust for multiple tests or multiple visits using a unique subject identifier. Multivariable model building and testing strategies used were similar to those described above for logistic regression.

Specific Aim 1:

This purpose of this aim was to examine the odds of preterm delivery among women before the availability of fetal fibronectin testing as compared to women after the availability of fetal fibronectin testing after adjusting for other variables in a logistic regression model. Using logistic regression, the outcome of preterm delivery, or delivery prior to 37 weeks was examined as a dichotomous variable comparing women delivering preterm with women delivering at term. The odds ratio of preterm delivery was calculated using women delivering at term as the reference group.

Using logistic regression to predict the odds of preterm delivery as the dichotomous dependent variable, univariate associations with the independent variables were examined for each cohort before (cohort for year 2000) and after (cohort for year 2001) fetal fibronectin testing using an SPSS option to split the file to provide separate analyses for each cohort. Final logistic regression models included the cohort 2000/2001 as a dichotomous variable as the exposure of interest in the model. Multivariable logistic regression models to predict preterm delivery were assessed independently for each cohort. Based on the univariable and age-adjusted analyses, as well as literature-based

associations, the following variables were included as candidate variables for further examination as confounders in the multivariable logistic regression model: maternal age, ethnicity, parity, history of preterm delivery, gestational age at first triage visit and number of triage visits. Maternal age was first entered in the model and candidate variables were tested in a stepwise fashion and retained if change in the coefficient was equal to or greater than 10%. In order to maintain comparability between the two years, if a candidate variable was retained in either model, it was included in both final models.

Correlations between the candidate variables were examined to identify potential multi-collinearity problems. Variables were entered in the model after testing the assumptions of linearity with the logit. After testing model assumptions, maternal age and gestational age at first triage visit were entered as continuous variables. Dummy variables were created for ethnicity using Caucasian as a reference category. Parity, history of preterm delivery, and triage visit (1 vs. >1) were entered as dichotomous variables. Product terms were entered in the models to test for interactions between variables.

Specific Aim 2:

The second aim was to examine the odds of admission to the neonatal intensive care unit (NICU) before and after the availability of fetal fibronectin testing after adjusting for other variables in a logistic regression model. Using logistic regression, the outcome of NICU or stepdown unit admission was examined as a dichotomous variable with normal nursery admission as the

reference as compared with neonates admitted to the NICU or stepdown nursery and the odds ratios were calculated.

Similar model building strategies previously described in Specific Aim 1 were used for Specific Aim 2. Odds ratios and 95% confidence intervals for univariate and gestational age at delivery -adjusted associations were calculated using logistic regression modeling. Multivariable logistic regression models to predict NICU admission were developed based upon the univariable, gestational age at delivery (age-adjusted), and literature based associations.

The following candidate variables were examined for inclusion in the multivariable logistic regression model: Group (reference 2000), gestational age at delivery, ethnicity (reference Caucasian), parity (reference nulliparous), history of preterm delivery (none), gestational age at first triage visit and number of triage visits (reference one visit). Group (2000/2001) and gestational age at delivery were first entered in the model and candidate variables were then tested in a stepwise fashion and retained if change in the coefficient was equal or greater than 10%.

A full logistic regression model to predict NICU admission before and after the availability of fetal fibronectin testing was developed. Correlations between the candidate variables were examined to identify potential multi-collinearity problems and no significant correlations among the candidate variables were identified.

Variables were entered in the model after testing the assumptions of linearity with the logit. The variable for cohort (2000/2001) was first entered in

the model. After testing model assumptions, gestational age at delivery was dichotomized using delivery at term as the reference as compared to preterm. Gestational age at first triage visit was entered as a continuous variable. History of preterm delivery (no versus yes), and triage visit (1 vs. >1) were entered as dichotomous variables. Product terms were entered in the models to test for interactions for between variables.

Specific Aim 3:

The third aim was to examine whether the availability of the assay had an effect on hospital services utilization (triage visits, admissions, and total length of stay) for the mothers and neonates. In addition, a secondary aim was to review the test attributes and results, the outcomes among the women who had fetal fibronectin testing and whether the test results influenced hospital admissions. This aim also compared those having the test to the baseline cohort attributes in a similar manner to specific aim 1 and specific aim 2 as described previously. Subject characteristics among those delivering preterm before and after test availability were compared to those who did and did not have fetal fibronectin testing.

Repeated measures Poisson regression models were developed to adjust for multiple visits and tests among subjects having fetal fibronectin testing in the 2001 cohort. A model to evaluate the relation between a positive test and cervical status was developed, as well as a model to calculate the odds of preterm delivery among those with a negative versus positive test.

A final Poisson model was developed to predict odds of hospital admission for subjects after adjusting for multiple visits, multiple tests, and test results in addition to other potential candidate variables. Variables included in the models were the exposure of interest (group) to examine the potential difference between the two cohorts, ethnicity using dummy variables using Caucasian as a reference, history of preterm delivery, gestational age at triage visit, maternal age, and cervical dilation >1.

CHAPTER 4

RESULTS

Characteristics of Study Sample

The subjects eligible for this study included women seen at 1,663 triage visits with signs and symptoms of preterm labor and “rule out preterm labor” diagnosis for six months prior to (800 visits) and six months after (863 visits) the availability of a rapid test for fetal fibronectin at a community based tertiary level hospital (Table 1). Approximately 30% of triage visits in each cohort failed to meet the inclusion criteria for the study (Table 2). The most frequent reasons for exclusion included failure to meet gestational age criteria (approximately 15% of each cohort), failure to deliver at same hospital (5-6%), multiple pregnancy (2-3%), and missing data, error in diagnosis, or records not available (2-2.5%). The final sample for this study included 762 subjects who had 1,157 triage visits for preterm labor in the six months prior to (372 subjects) and after (390 subjects) which comprises approximately 70% of the triage visits for rule out preterm labor during the study period. A total of 215 fetal fibronectin tests were performed on 183 patients; with 157 patients with one test, 21 patients with two tests, 4 patients with three tests, and 1 patient with four tests. Among subjects eligible for fetal fibronectin testing in the 2001 cohort, 47 percent (183/390) received the test.

Table 1. Selection of Study Subjects

	Before FFN 2000	After FFN 2001	Total
Triage visits for "rule out preterm labor	800	863	1663
Triage visits not meeting inclusion/exclusion	244	262	506
Number of qualifying triage visits	556	601	1157
Number of study subjects with at least one qualifying triage visit	372	390	762
Fetal fibronectin testing			
Number of subjects with fetal fibronectin testing		183	
Number of subjects with one fetal fibronectin test		157	
Number of subjects with repeated testing 2 tests = 21 subjects 3 tests = 4 subjects 4 tests = 1 subject		26	
Total fetal fibronectin tests performed			215

Table 2. Selection of qualifying triage visits for study subjects. Women presenting to triage with "rule out preterm labor" diagnosis before and after test availability.

	2000 Before FFN		2001 After FFN	
Number of triage visits (n=1663)	n=800		n=863	
Reason for exclusion	n	%	n	%
Gestational age criteria not met	123	(15.4)	129	(14.9)
Did not deliver at same hospital	40	(5.0)	51	(5.9)
No triage visit record, unable to obtain data, error in diagnosis	20	(2.5)	18	(2.1)
Multiple pregnancy	23	(2.9)	17	(2.0)
No contraction activity	3	(0.3)	8	(0.9)
PPROM documented	8	(1.0)	12	(1.4)
Preeclampsia	3	(0.3)	7	(0.8)
Bleeding, abruption	5	(0.6)	7	(0.8)
Dilated greater than 3.0 cm	3	(0.4)	7	(0.8)
No cervical exam at triage	7	(0.9)	1	(0.1)
Kidney stone, pyelonephritis	2	(0.3)	3	(0.3)
Cervical exam in intercourse in past 24 hours	3	(0.4)	0	
Trauma, MVA	3	(0.4)	1	(0.1)
Cerclage	1	(0.1)	1	(0.1)
Total Visits Excluded Total triage visits excluded 506/1663=30.43%	244	(30.5)	262	(30.4)

Maternal and Pregnancy Characteristics

Comparison of the baseline maternal demographic characteristics between the two groups (Table 3) revealed similar demographic and pregnancy characteristics between the first (2000) and second (2001) cohorts. The mean maternal age at the time of qualifying triage visit for the two cohorts was 31.50 ± 6.1 for 2000, as compared to 30.47 ± 6.3 for 2001. Categorization of maternal age for further examination revealed a higher percentage of women greater than 34 years in the 2000 cohort as compared to the 2001 cohort (30.9% versus 26.2%) as well as a lower percentage of women 16-24 years in the 2000 cohort (14.0% versus 20.5%). The ethnic composition of the cohorts was comparable.

The number of previous pregnancies, parity, and history of preterm delivery were similar in both cohorts (Table 4, Table 5). The mean gestational age at the time of the first triage visit was 29.7 ± 3.0 for the 2000 cohort and 30.3 ± 2.9 for the 2001 cohort (Table 5). Pregnancy outcome and summary characteristics revealed comparable gestational age delivery, birth weight, and number of triage visits (Table 4, Table 5).

Table 3. Description of study subjects: maternal demographic characteristics before and after the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

	2000		2001		pvalue
Number of subjects	n= 372		n= 390		
	(mean±sd)		*(mean±sd)*		
Maternal age at triage visit 1	31.5 ± 6.1		30.47 ± 6.3		0.021[a]
Gestational age at triage visit 1	29.7 ± 3.0		30.30 ± 2.9		0.008[a]
	n	*%*	*n*	*%*	
Maternal age at triage visit 1					
16 - 24 years	52	(14.0)	80	(20.5)	0.04[b]
25 - 34 years	205	(55.1)	208	(53.3)	
> 34 years	115	(30.9)	102	(26.2)	
Ethnicity					
Caucasian	205	(56.3)	220	(58.2)	0.20[b]
Hispanic	90	(24.7)	71	(18.7)	
African American	25	(6.9)	32	(8.5)	
Asian	44	(12.1)	55	(14.6)	
Other/missing	*8*		*12*		

[a]t-test [b]chi-square test

Table 4. Description of study subjects: maternal pregnancy characteristics at first triage visit before and after the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

	2000		2001		pvalue
Number of subjects	n=372		n=390		
	n	(%)	n	(%)	
Number of previous pregnancies (Gravidity)					
None	88	(23.7)	111	(28.5)	0.32[b]
1	105	(28.2)	111	(28.5)	
2	77	(20.7)	89	(22.8)	
3 or more	102	(27.4)	79	(20.2)	
Number of previous pregnancies					
None	88	(23.7)	111	(28.5)	0.13[b]
Parity					
Nulliparous	132	(35.5)	161	(41.3)	0.10[b]
Multiparous	240	(64.5)	229	(58.7)	
Number previous preterm deliveries					
None	319	(85.8)	339	(87.0)	0.67[b]
1	44	(11.8)	38	(9.7)	
2 or more	9	(2.4)	13	(3.3)	
History of preterm delivery	53	(14.2)	51	(13.1)	0.64[b]
Gestational age at triage visit 1					
24.0 to 28.0	113	(30.3)	94	(24.1)	0.09[b]
28.1 to 32.0	149	(40.1)	157	(40.3)	
32.1 to 34.6	110	(29.6)	139	(35.6)	

[a]t-test [b]chi-square test

Table 5. Pregnancy outcome information before and after availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

	2000 n=372		2001 n=390		p value
Total number of triage visits	556		601		
	(mean±sd)		*(mean±sd)*		
Gestational age at delivery	38.3 ± 1.89		38.4 ± 1.89		0.90[a]
Gestational age at triage visit 1	29.7 ± 3.0		30.3 ± 2.90		0.008[a]
	n	*%*	*n*	*%*	
Subjects with 1 visit	372	(66.9)	390	(64.9)	0.12[b]
2 visits	122	(21.9)	145	(24.1)	
3 visits	47	(8.5)	42	(7.0)	
>=4 visits	15	(2.7)	24	(4.0)	
Number of triage visits					
One visit	241	(64.8)	260	(66.7)	0.59 [b]
>1 visit	131	(35.2)	130	(33.3)	
Term delivery	245	(65.9)	265	(67.9)	0.54[b]
Preterm delivery					
Total deliveries ≤ 37wks	126	(33.9)	124	(31.8)	0.54[b]
Delivery ≤ 32w6d	4	(3.1)	6	(4.8)	0.06[d]
Between 33w0d and 35w6d	31	(24.4)	21	(16.8)	0.10[b]
Between 36w0d and 36w6d	35	(27.6)	29	(23.2)	0.33[b]
Between 37w0d and 37w6d	56	(44.9)	68	(55.2)	0.37[b]
Birth weight					
ELBW < 1000 grams	0		1	(0.3)	0.50[d]
VLBW < 1500 grams	0		4	(1.0)	0.12[d]
LBW < 2500 grams	34	(9.1)	20	(5.1)	0.04[b]
*2501 to 3000 grams	56	(15.1)	81	(20.8)	0.05 [b]
3001 to 4000 grams	238	(64.0)	262	(67.2)	0.42 [b]
>4000 grams	43	(11.6)	22	(5.6)	0.005[b]
Missing	*1*	*(0.3)*	*0*		

[a]t-test [b]chi-square test [d]Fisher's Exact Test *birth weight 2500 = 5.5 pounds

Specific Aim 1

Descriptive and Univariable Analyses

Sample size and characteristics of women delivering preterm are presented in Table 6. There were 126 (33.9%) women delivering preterm in the 2000 cohort and 124 (31.8%) in the 2001 cohort. Univariable unadjusted associations with preterm delivery are presented in Appendix A, Table A1. Maternal age-adjusted measured of association to predict preterm delivery in the two cohorts (2000, 2001) before and after the availability of fetal fibronectin testing are presented in Table 7. Age-adjustment did not significantly attenuate, strengthen or change the direction of measured associations.

Table 6. Sample characteristics of women delivering preterm before and after the availability of fetal fibronectin testing.

	2000 (n=372)		2001 (n=390)		
	Mean, sd		*Mean, sd*		*pvalue*
Maternal age	31.9 ± 6.3		30.6 ± 6.8		0.13 [a]
Gestational age Triage V1	30.0 ± 3.1		30.1 ± 3.0		0.92 [a]
	n	*%*	*n*	*%*	
Preterm Delivery	126	(33.9)	124	(31.8)	0.54 [b]
Ethnicity					
White	70	(56.9)	77	(64.2)	0.65 [b]
Hispanic	28	(22.8)	24	(20.0)	
African American	11	(8.9)	7	(5.8)	
Asian	14	(11.4)	12	(10.0)	
missing	*4*		*5*		
Parity (nulliparous)	36	(28.3)	49	(39.2)	0.07 [b]
Previous PTD (No)	94	(74.0)	94	(75.2)	0.83 [b]
Number Triage visits (1)	74	(58.3)	75	(60.0)	0.78 [b]

[a] t-test [b] chi-square test

Table 7. Univariable and maternal age adjusted measures of association with preterm delivery before and after the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

	2000 (n=372)		2001 (n=390)	
Preterm Delivery (n, %)	126 (33.9)		124 (31.8)	
	OR (95% CI)	Age Adjusted OR (95% CI)	OR (95% CI)	Age Adjusted OR (95% CI)
Ethnicity				
White (reference)	1.0	1.0	1.0	1.0
Hispanic	0.87 (0.51, 1.48)	0.90 (0.52, 1.55)	0.95 (0.54, 1.67)	0.96 (0.55, 1.70)
African American	1.51 (0.65, 3.51)	1.61 (0.68, 3.82)	0.52 (0.21, 1.26)	0.53 (0.22, 1.29)
Asian	0.90 (0.45, 1.81)	0.90 (0.45, 1.81)	0.52 (0.26, 1.04)	0.52 (0.26, 1.04)
Nulliparous	1.63 (1.03, 2.59)*	1.61 (0.99, 2.61)	1.14 (0.74, 1.75)	1.13 (0.72, 1.76)
Previous preterm delivery	3.95 (2.16, 7.24)***	3.96 (2.14, 7.35)***	4.04 (2.19, 7.44)***	4.08 (2.20, 7.54)***
Gestational age Triage V1	1.04 (0.97, 1.12)	1.04 (0.97, 1.12)	0.96 (0.89, 1.03)	0.96 (0.89, 1.03)
Number Triage visits =1	1.53 (0.98, 2.39)	1.52 (0.97, 2.37)	1.54 (0.99, 2.40)	1.55 (0.99, 2.41)

* p< .05, ** p< .01, ***p< .001

Multivariable Analyses

Full logistic regression models to predict preterm delivery for the 2000 and 2001 cohorts separately are presented in Appendix A, Table A1, Table A2 and the reduced models are presented in Appendix A, Table A3 for the 2000 cohort and Appendix A, Table A4 for the 2001 cohort.

The full logistic regression model including the cohort 2000/2001 in the model is presented in Table 8 and the final reduced model is presented in Table 9. In the final model, the risk of delivering preterm was 3.85 times more likely (95% CI 2.49, 5.98) among women with a history or preterm delivery after adjusting for group, maternal age, and triage visits. The risk of delivering preterm was 1.4 times (95% CI 1.02, 1.94) more likely among women with more than one triage visit after adjusting for group, maternal age, and history of preterm delivery. Collinearity was assessed using multiple linear regression and results did not suggest a collinearity problem with the final model. The Hosmer and Lemshow goodness of fit test for the final model revealed a chi square statistic of 3.96 with 8 degrees of freedom, p= 0.86, suggesting the model was a good fit at alpha = 0.10.

Table 8. Full logistic regression model to predict preterm delivery before and after the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-1.86	0.98	0.06		
Group 2000 (reference)	-0.10	0.16	0.53	0.90	0.65, 1.25
Maternal age (one year increase)	-0.003	0.01	0.83	0.99	0.97, 1.03
Parity (reference nulliparous)	-0.03	0.19	0.88	0.97	0.68, 1.39
Previous preterm delivery (reference no)	1.40	0.24	<0.001	4.06	2.56, 6.45
Gestational age Triage visit 1	0.04	0.03	0.22	1.04	0.98, 1.09
Number triage visits (reference 1 visit)	0.37	0.18	0.04	1.45	1.03, 2.05
Ethnicity					
Caucasian (reference)					
Hispanic	-0.15	0.21	0.49	0.86	0.57, 1.30
African American	-0.13	0.32	0.69	0.88	0.47, 1.65
Asian	-0.41	0.19	0.12	0.67	0.40, 1.11

Table 9. Final logistic regression model to predict preterm delivery before and after the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-0.91	0.43	0.03		
Group (reference 2000)	-0.08	0.16	0.62	0.92	0.68, 1.26
Maternal age (1 year increase)	-0.003	0.01	0.84	0.99	0.97, 1.02
Previous preterm delivery (reference no)	1.35	0.22	<0.001	3.85	2.49, 5.98
Triage visits (reference 1 visit)	0.34	0.17	0.04	1.4	1.02, 1.94

Specific Aim 2

Descriptive and Univariable Analyses

Sample size and characteristics among subjects with neonatal intensive care admission before and after the availability of fetal fibronectin testing are presented in Table 10. Univariable measures of association with NICU admission are presented in Appendix A, Table A5. Gestational ages at delivery-adjusted measures of association are presented in Appendix A, Table A6. There were 36 (9.7%) NICU admissions in the 2000 cohort, and 35 (9.0%) in the 2001 cohort. Univariable measures of association were similar between the two cohorts after adjusting for gestational age at delivery. (Appendix A, Table A6).

Table 10. Sample characteristics of subjects with neonatal intensive care admission before and after the availability of fetal fibronectin testing.

	2000 (n=372)		2001 (=390)		
	n	*%*	*n*	*%*	*pvalue*
NICU/stepdown admissions	36	(9.7)	35	(9.0)	0.74[b]
Gestational age at delivery					
Term	13	(36.1)	13	(37.1)	0.93 [b]
Maternal age (categories)					
16 - 24	5	(13.9)	6	(17.1)	0.24 [b]
25 - 34 years (reference)	20	(55.5)	13	(37.2)	
>= 35	11	(30.6)	16	(45.7)	
Ethnicity					
White (reference)	21	(63.7)	22	(66.8)	0.76 [b]
Hispanic	7	(21.3)	7	(21.2)	
African American	2	(6.0)	3	(9.0)	
Asian	3	(9.0)	1	(3.0)	
Parity (nulliparous)	14	(38.9)	13	(37.1)	0.95 [b]
Previous preterm delivery (no)	27	(75.0)	26	(74.3)	0.90 [b]
Gestational age Triage V1					
24.0 to 28.0	13	(36.1)	10	(28.6)	0.57 [b]
28.1 to 32.0	8	(22.2)	11	(31.4)	
32.1 to 34.6	15	(41.7)	14	(40.0)	
Number Triage visits (1)	24	(66.7)	27	(77.1)	0.37 [b]
	mean, sd		*mean, sd*		
Maternal age	31.3 ± 5.9		32.1 ± 6.5		0.59 [a]

[a] t-test [b] chi-square test

Multivariable Analyses

The full logistic regression model to predict the odds of NICU admission is presented in Table 11. After inclusion of the variables for cohort 2000/2001 and gestational age at delivery, candidate variables included for consideration in the full model were history of preterm delivery, gestational age at triage visit 1, and total number of triage visits.

The final reduced model to predict NICU admission is presented in Table 12. No association was seen between NICU admission and the exposure of interest (group) representing the 2000 cohort as the reference versus the 2001 cohort (OR 1.04, 95% CI 0.61, 1.8). After adjusting for cohort and gestational age at delivery, the risk of NICU admission was 0.54 times as likely among women with more than one triage visit (95% CI 0.30, 0.99) as compared to women with one triage visit. Collinearity in the final model was assessed and results did not suggest collinearity problems with the final models. The Hosmer and Lemeshow goodness of fit test for the final model revealed a chi square statistic of 0.81 with 3 degrees of freedom and p= 0.85, suggesting the model was a good fit at alpha= 0.10.

Table 11. Full logistic regression model to predict NICU admission before and after the availability of a test for fetal fibronectin among women with signs and symptoms of preterm labor.

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-2.24	1.5	0.13		
Group 2000 (reference)	0.03	0.28	0.92	1.03	0.60, 1.8
Gestational age at delivery (reference term)	2.62	0.29	<0.001	13.8	7.90, 24.2
Previous preterm delivery (reference no)	0.30	0.34	0.38	1.4	0.69, 2.6
Gestational age Triage visit 1	-0.03	0.05	0.59	0.98	0.69, 2.6
Total number Triage visits (reference 1)	-0.71	0.33	0.03	0.49	0.26, 0.93

Table 12. Final logistic regression model to predict NICU admission before and after the availability of a test for fetal fibronectin among women with signs and symptoms of preterm labor.

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-3.01	0.26	<0.001		
Group 2000 (reference)	0.04	0.28	0.89	1.04	0.61, 1.8
Gestational age at delivery (reference term)	2.67	0.28	<0.001	14.5	8.40, 25.0
Number of triage visits (reference 1)	-0.61	0.30	0.05	0.54	0.30, 0.99

Specific Aim 3

Outcomes and Hospital Based Services

Comparison of outcomes and utilization of hospital-based services is presented in Table 13a. The mean number of days from the time of qualifying triage visit to delivery was (60.3 ± sd 25.2, 56.36 ± sd 23.5) for the 2000 and 2001 cohorts respectively. This relation was not statistically significant after adjusting for gestational age at triage (Table 13b) in a logistic regression model. The percentage of subjects with maternal total hospital length of stay less than or equal to three days was 94.4% for 2000 and 93.6% for 2001. In the 2000 cohort, 2.2% received antenatal steroids and 3.1% received antenatal steroids in 2001. The percentage of subjects admitted for preterm labor from triage was 14.8% (n=55) in 2000 and 21.2% (n=83) in 2001.

Table 13a. Comparison of outcome and utilization of hospital based services among women with signs and symptoms of preterm labor before and after the availability of fetal fibronectin test.

Variable	2000		2001		p value
Subjects	(n=372)		(n=390)		
	mean ± sd		*mean ± sd*		
Days to delivery	60.3	(25.2)	56.36	(23.5)	0.03[a]
Number triage visits	1.54	(0.91)	1.48	(0.91)	0.34[a]
	n	*%*	*n*	*%*	
Total length of stay (maternal)					
0 to 3 days	351	(94.4)	365	(93.6)	0.66[b]
Maternal total hospital stay					
0 – 1 day	131	(35.2)	110	(28.2)	0.33[b]
2-3 days	179	(48.1)	203	(52.1)	
4-5 days	41	(11.0)	52	(13.3)	
6-14 days	18	(4.8)	21	(5.4)	
≥ 15 days	3	(0.8)	4	(1.0)	
Antenatal steroids administered	8	(2.2)	12	(3.1)	0.50[c]
Maternal hospital admissions					
For preterm labor from triage visit	55	(14.8)	83	(21.2)	0.11[b]

[a]t-test [b]chi-square test [c] Fisher's exact test

Table 13b. Logistic regression model to predict group 2000 versus 2001 and days to delivery after triage visit after adjusting for gestational age at triage visit.

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-1.91	1.62	0.24		
Days to delivery	0.00	0.006	0.99	1.0	0.99, 1.01
Gestational age	0.07	0.05	0.15	1.07	0.98, 1.06

Comparison of neonatal outcome and hospital-based services are presented in Table 14. The mean gestational age at delivery was 38.3 and 38.4 respectively for 2000 and 2001 and did not differ (p=0.89). Stratification of neonatal length of stay did not reveal statistically significant differences between the cohorts. They were also comparable for other parameters including the proportion receiving surfactant (1.9%, 2.3% p= 0.43) ventilation required (4.5%, 6.9%, p= 0.16), intraventricular hemorrhage (0.5%, 0%, p= 0.24) and respiratory distress syndrome (2.2%, 1.8%, p= 0.79). There were 51% males in the 2000 cohort and 52% in the 2001 cohort.

Table 14. Comparison of neonatal outcome and utilization of hospital based services before and after the availability of fetal fibronectin test among women with signs and symptoms of preterm labor.

Variable	2000	2001	p value
	n=372	n=390	
	mean±sd	*mean±sd*	
Gestational age at delivery	38.3 (1.9)	38.4 (1.9)	0.89[a]
	n %	*n* %	
Neonatal gender			
Male	191 (51)	201 (52)	0.95[b]
Female	181 (49)	189 (48)	
Neonatal length of stay			
1-2 days	233 (62.6)	264 (67.7)	0.47[b]
3-4 days	100 (26.9)	92 (23.6)	
5-10 days	28 (7.5)	20 (5.1)	
11-30 days	7 (1.9)	9 (2.3)	
31-61 days	4 (1.1)	5 (1.3)	
Neonates receiving surfactant	7 (1.9)	9 (2.3)	0.43[d]
Neonatal ventilation required	17 (4.5)	27 (6.9)	0.16[b]
Neonatal intraventricular hemorrhage	2 (0.5)	0 (0)	0.24[d]
Neonatal respiratory distress syndrome	8 (2.2)	7 (1.8)	0.79[d]

[a]t-test [b]chi-square test [c]Mann-Whitney Wilcoxin Rank Sum test, [d]Fisher's Exact Test

Table 15 presents a logistic regression model to more closely examine the relation between the two cohorts before (2000) and after (2001) the availability of fetal fibronectin and neonatal length of stay. There were no significant differences between lengths of stay between the two cohorts after adjusting for gestational age at delivery.

Table 15. Logistic regression model and gestational age at delivery adjusted model to compare neonatal length of stay before (2000) and after (2001) the availability of fetal fibronectin test among women with signs and symptoms of preterm labor.

Variable	Beta	SE	p value	OR	95% CI	Gestational Age-adjusted OR	(95% CI)
Neonatal length of stay							
1-2 days (reference)							
3-4 days	-0.22	0.17	0.19	0.80	0.58, 1.12	0.81	0.58, 1.13
5-10 days	-0.46	0.31	0.13	0.63	0.35, 1.15	0.65	0.35, 1.19
11-30 days	0.13	0.51	0.81	1.14	0.42, 3.10	1.20	0.43, 3.37
31-61 days	0.10	0.09	0.89	1.10	0.29, 4.16	1.17	0.30, 4.49

Sensitivity, Specificity, Positive and Negative Predictive Values

The sensitivity, specificity, positive and negative predictive values for the fetal fibronectin test were calculated using preterm delivery within 14 days of fetal fibronectin testing as the outcome of interest (Table 16). Using the number of tests (n=215) for the calculations, the sensitivity for the test was 100% (3/3), specificity 92.9% (197/212), positive predictive value 16.7% (3/18), and negative predictive value 100% (197/197).

Table 16. Sensitivity, specificity, positive and negative predictive value for preterm delivery within 14 days of fetal fibronectin testing – all tests (n=215) for 183 subjects.

	Delivered < = 14 days	Delivered > 14 days	Total
Fetal fibronectin test results			
Test Positive	3	15	18
Test Negative	0	197	197
Total	3	212	215

Sensitivity = 3/3 = 100
Specificity = 197/212= 92.9
Positive predictive value= 3/18= 16.7
Negative predictive value = 197/197= 100

Fetal Fibronectin Testing

Table 17 presents a summary of the utilization history of the number of fetal fibronectin tests and the number of qualifying triage visits for the first six months of testing. The total number of patients having at least one triage visit after test availability was 390 in the 2001 cohort. The number of tests divided by the number of visits for each month reveals increasing test utilization percentages during the six-month study interval with a significant trend ($p < 0.001$). Total number of patients with at least one triage visit during test availability period (2001) was 390.

Table 17. Test utilization summary of fetal fibronectin testing among women presenting with signs and symptoms of preterm labor (2001).

Number of tests per month		Qualifying visits	Tests/visits %
1.	26	98	26/ 98=27%
2.	35	119	35/119=29%
3.	29	86	29/ 86=34%
4.	36	110	36/110=33%
5.	41	84	41/ 84=49%
6.	48	104	48/104=46%
Total	215	601	215/601=36%

Chi square for trend =17.34, p < 0.001

Table 18 presents descriptive information and results among the 183 subjects having at least one fetal fibronectin test during the 2001 study period. Among the 215 tests performed, 92% (197) tests were negative, and 8% (18) tests were positive. A total of 153 subjects had one fetal fibronectin test, and 26 had multiple fetal fibronectin tests. Among those with multiple tests, 81% (21) had two tests, 15% (4) had three tests, and 4% (1) had four tests. Among the 18 subjects ultimately having a positive fetal fibronectin test, 67% (12) of the

subjects had a positive test at their first triage visit, 17% (3) at their second visit, 11% (2) at their third visit, and 5% (1) had a positive test at the fourth triage visit.

Table 18. Fetal fibronectin testing descriptive information and results.

Total number fetal fibronectin tests performed	215
Negative = 197	
Positive = 18	
Number of subjects having fetal fibronectin testing	183
Number of subjects with one test	153
Number of subjects with repeat testing	26
2 tests = 21 patients	
3 tests = 4 patients	
4 tests = 1 patient	
Triage visit number resulting in positive fetal fibronectin test	
Positive test at triage visit number 1 (n)	12
Positive test at triage visit number 2 (n)	3
Positive test at triage visit number 3 (n)	2
Positive test at triage visit number 4 (n)	1
Total positive tests	18

A summary of characteristics, treatments, and outcomes for subjects having a positive test at their first visit (n=12) is presented in Table 19. The gestational age range at the time of positive test was 25.2 to 34.0 weeks gestation. A total of 42% (n=5) subjects with a positive test were admitted to the hospital and 59% (n=7) were not admitted. There were no deliveries within 14 days among the 12 subjects with a positive test at their first visit, however, 50% (n=6) subjects ultimately delivered prior to completion of 37 weeks gestation.

Table 19. Summary of fetal fibronectin positive subjects at first test (n=12).

Case	Gestational age at test	Cervical dilation	Test results	Steroids given	Gestational age at delivery	Days from test to delivery	History PTD preterm delivery	Admitted after test
1.	31.4	0	Pos	No	36.6	36	0	No
2.	25.2	0	Pos	No	41.0	110	0	No
3.	26.3	ND	Pos	No	33.0	47	3	Yes
4.	28.3	0.5	Pos	No	39.6	79	0	Yes
5.	31.3	1.5	Pos	No	36.4	34	0	Yes
6.	26.4	1.0	Pos	No	37.2	76	1	Yes
7.	34.0	0	Pos	Yes	39.5	39	0	No
8.	33.0	2.0	Pos	No	36.0	21	0	No
9.	32.2	2.0	Pos	Yes	37.4	36	0	No
10.	26.6	0	Pos	Yes	38.4	83	1	No
11.	29.0	1.5	Pos	Yes	31.3	16	1	No
12.	30.0	0	Pos	No	33.4	24	0	Yes

Gestational age at test = Gestational age at time of fetal fibronectin testing
Cervical dilation = Cervical dilation at triage visit in centimeters, ND= cervical exam not done
Test results = fetal fibronectin test results, Neg= Negative Pos=Positive
Steroids given = No or yes, glucocorticoids administered to subject to hasten fetal lung maturity
Gestational age at delivery
Days from test to delivery= days from fetal fibronectin testing to delivery
Admitted after test= Subject admitted to the hospital for observation after fetal fibronectin testing.

Six subjects had a positive fetal fibronectin test after having multiple tests. Table 20 presents the characteristics, test results, and treatments for each triage visit among subjects having a positive test after repeated testing (n=6). Sixty-seven percent (n=4) of the subjects had a history of a previous preterm delivery. Only 17% (n=1) of the subjects was administered antenatal steroids at the time of positive test, however, one subject was given steroids after a negative test at their first visit. Among the six subjects having a positive test after multiple tests, 50% (3) delivered within 14 days of the positive test. A total of 67% (4 of 6) subjects with a positive test after multiple tests delivered prior to completion of 37 weeks.

Table 20. Summary of patients with positive fetal fibronectin test after multiple tests (n=6).

Case Number	Number Triage Visits	Gestational age at test	Cervical dilation*	Test results*	Steroids given*	Gestational age at delivery	Days to delivery*	History Preterm delivery*
1.	1	29.5	1.5	Neg	Yes	37.5	31	No
	2	33.1	2.5	Pos	No			
2.	1	32.0	1.5	NR	No	38.2	43	3
	2	32.1	1.5	Pos	No			
3.	1	27.4	1.0	Neg	No	34.2	7	1
	2	33.2	1.5	Pos	No			
4.	1	30.5	0	NR	No	35.0	9.8	1
	2	30.6	0.5	Neg	No			
	3	33.5	1.0	Neg	No			
	4	33.6	1.5	Pos	Yes			
5.	1	32.4	1.0	Neg	No	35.5	8	0
	2	32.5	1.0	Neg	No			
	3	34.4	1.5	Pos	No			
6.	1	29.4	1.0	Neg	No	36.6	16	2
	2	30.5	1.0	Neg	No			
	3	30.6	1.0	NR	No			
	4	34.3	1.5	Pos	No			

*Cervical dilation in centimeters at time of fetal fibronectin testing,
*Test results= Fetal fibronectin test results, Neg=Negative, Pos= Positive, NR= test not run
*Steroids= antenatal glucocorticoids administered to subject to hasten lung maturity No= no steroids given, Yes= steroids given
*Days to delivery= days from fetal fibronectin testing to delivery *History preterm delivery= number of previous preterm deliveries

The data presented in Table 21 allows comparison of hospital admission and fetal fibronectin test results for all 215 fetal fibronectin tests (n=183 patients). Among the 18 positive tests, only 50% (n=9) were admitted to the hospital for further evaluation and observation. Among the 197 negative tests, 14% (n=28) were admitted to the hospital. Using patient hospital admission at time of triage visit as the outcome predicted by fetal fibronectin test results, the sensitivity was 24%, specificity 95%, positive predictive value 50%, and negative predictive value 86%.

Table 21. Sensitivity, specificity, positive and negative predictive value for hospital admission after fetal fibronectin testing (183 patients, 215 tests).

		Patient admitted to hospital after test		
		Yes	No	Total
Fetal fibronectin test results	Positive	9	9	18
	Negative	28	169	197
		37	178	215

Sensitivity = 9/37= 24%
Specificity = 169/178= 95%
Positive predictive value= 9/18= 50%
Negative predictive value = 169/197 = 86%

Cervical dilation in centimeters as compared with fetal fibronectin test results for all 215 tests is presented in Table 22. Among the 17 positive tests with a corresponding cervical examination, 65% (n=11) were dilated to at least 1.0 centimeters, as compared to 25% of those with a negative test (n=45).

Table 22. Cervical dilation at time of fetal fibronectin testing and test results. (all tests n=215).

	Cervical dilatation*			
	0 to 0.5	1.0 to 2.0	2.5 to 3.0	Total
Fetal fibronectin				
Positive	6	10	1	17
Negative	138	42	3	183
Total	144	52	4	200

*Cervical dilation missing n=15

Cohort Comparisons

Tables 23a and 23b present subject characteristics and outcomes for the 2000 (n=372) and 2001 (n=390) cohorts as well as further stratification of subjects in the 2001 cohort who had fetal fibronectin testing (n=183) and did not have fetal fibronectin testing (n=207). There were no differences in characteristics and outcomes among subjects who had fetal fibronectin testing as compared to the 2000 baseline cohort as the reference group, or when compared to subjects who did not have fetal fibronectin testing as the reference group.

Table 23a. Subject characteristics and preterm delivery before and after test availability as compared to those who did and did not have testing.

	2000	2001	FFN test	No FFN test	1pvalue	2pvalue
Number of patients	n= 372	n= 390	n=183	n=207		
	n, %	*n, %*	*n, %*	*n, %*		
Preterm delivery <37weeks	127 (34.1)	125 (32.1)	61 (33.3)	64 (30.9)	0.92 [b]	0.69 [b]
	(mean±sd)	*(mean±sd)*	*(mean±sd)*	*(mean±sd)*		
Maternal age at triage visit 1	31.5 (6.1)	30.47 (6.3)	31.0 (2.7)	30.8 (6.2)	0.18 [a]	0.67 [a]
Gestational age at triage visit 1	29.7 (3.0)	30.3 (2.9)	30.0 (3.1)	30.1 (2.7)	0.27 [a]	0.74 [a]
Days from test to delivery	43.9 (23.8)	43.6 (22.1)	45.7 (18.9)	41.7 (23.9)	0.33 [a]	0.07 [a]
	n,%	*n,%*	*n,%*	*n,%*		
Ethnicity						
Caucasian	70 (56.9)	77 (64.2)	40 (65.6)	37 (62.7)	0.46 [b]	0.39 [b]
Hispanic	28 (22.8)	24 (20.0)	8 (13.1)	16 (27.1)		
African American	11 (8.9)	7 (5.8)	5 (8.2)	2 (3.4)		
Asian	14 (11.4)	12 (10.0)	8 (13.1)	4 (6.8)		
Other/missing (excluded)	*4*	*5*	*3*	*2*		
Nulliparous	36 (28.3)	49 (39.2)	26 (40.6)	23 (37.7)	0.17 [b]	0.47 [b]
History of preterm delivery (no)	94 (74.0)	94 (75.2)	44 (68.8)	50 (82.0)	0.83 [b]	0.97 [b]

1p value compares fetal fibronectin test group versus reference 2000 cohort
2 p value compares fetal fibronectin test group versus no test group
[a]t-test [b]chi-square test

Table 23b. Subject characteristics and preterm delivery before and after test availability as compared to those who did and did not have testing.

	2000	2001	FFN test	No FFN test	1 pvalue	2 pvalue
Number of patients	n= 372	n= 390	n=183	n=207		
	n, %	*n, %*	*n, %*	*n, %*		
Preterm delivery <37weeks	127 (34.1)	125 (32.1)	61 (33.3)	64 (30.9)	0.92 [b]	0.69 [b]
Number Triage visits (1)	74 (58.3)	75 (60.0)	41 (64.1)	34 (55.7)	0.56 [b]	0.08 [b]
Total maternal length of stay 0 to 3 days	113 (88.9)	107 (85.6)	53 (82.8)	54 (88.5)	0.81 [b]	0.60 [b]
NICU Admissions	36 (28.3)	35 (28.0)	19 (29.7)	16 (26.2)	0.91 [b]	0.46 [b]

1p value compares fetal fibronectin test group versus reference 2000 cohort
2 p value compares fetal fibronectin test group versus no test group
[a]t-test [b]chi-square test

Repeated Measures Model to Predict Odds of Positive Test

Table 24 presents a Poisson regression model to predict the odds of positive fetal fibronectin test based upon cervical status after adjusting gestational age at triage and multiple tests. Subjects with cervical dilation of less than or equal to 1 centimeter were 0.74 times (OR 0.74, p=0.001, 95% CI 0.62, 0.89) more likely to have a positive fetal fibronectin test after adjusting for gestational age at triage and multiple tests.

Table 24. Poisson regression model to predict odds of positive fetal fibronectin test and relation with cervical status for subjects (n=183) at the time of fibronectin testing (n=215 tests) after adjusting for multiple tests.

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	0.47	0.22	0.03		
Gestational age at triage	-0.004	0.01	0.49	0.99	0.98, 1.01
Cervical status <=1	-0.29	0.09	0.001	0.074	0.62, 0.89

Cervical dilation missing n=15.

Repeated Measures Model to Predict Preterm Delivery

Tables 25a and 25b present full and reduced Poisson regression models to predict the odds of preterm delivery among those having a fetal fibronectin testing after adjusting for multiple tests. The odds of preterm delivery was 2.21 times (p=<0.001, 95% CI 1.58, 3.11) more likely among women with a history of preterm delivery after adjusting for gestational age at test, patient admission from triage, and multiple tests. The odds of preterm delivery was 1.71 times (p=.004, 95% CI 1.19, 2.46) more likely among women who were admitted from triage after adjusting for gestational age at test, history of preterm delivery, and multiple tests.

Table 25a. Full Poisson regression model to predict risk of preterm delivery among subjects (n=183) having fetal fibronectin testing (n=215 tests) after adjusting for multiple tests.

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-1.06	1.2	0.39		
Gestational age at test	-0.002	0.04	0.96	0.99	0.92, 1.07
Fetal fibronectin positive	-0.05	0.29	0.87	0.95	0.54, 1.69
Maternal age	0.004	0.02	0.79	1.004	0.97, 1.04
Multiparous	-0.27	0.22	0.23	0.76	0.49, 1.18
Ethnicity					
Caucasian (ref)					
Hispanic	-0.01	0.27	0.97	0.99	0.58, 1.69
African American	-0.23	0.31	0.46	0.79	0.44, 1.46
Asian	-0.32	0.30	0.29	0.73	0.40, 1.31
History of preterm delivery	0.89	0.20	<0.001	2.43	1.63, 3.62
Patient admitted from triage	0.56	0.21	0.009	1.76	1.15, 2.67

Table 25b. Final Poisson regression model to predict risk of preterm delivery among subjects (n=183) having fetal fibronectin testing (n=215 tests) after adjusting for multiple tests.

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-1.41	1.08	0.18		
Gestational age at test	0.007	0.04	0.83	1.007	0.94, 1.08
History of preterm delivery	0.79	0.17	<0.001	2.21	1.58, 3.11
Patient admitted from triage	0.54	0.18	0.004	1.71	1.19, 2.46

Repeated Measures Model to Predict Hospital Admission

Table 26 presents a Poisson regression model to predict risk of hospital admission for all subjects (762) after adjusting for multiple triage visits. The exposure of interest (group) was modeled using the reference cohort for the 2000 cohort as compared to the 2001 cohort after test availability. In the reduced model, no relation was seen between risk of hospital admission between the two groups (OR = 0.98, p= 0.98, 95% CI 0.94, 1.02) after adjusting for multiple visits, maternal age, gestational age at triage visit, cervical dilation and fetal fibronectin test results.

Women with no history of preterm delivery were 0.91 times more likely to be admitted to the hospital (p= 0.007, 95% CI 0.86, 0.98) after adjusting for multiple visits, group, maternal age, gestational age at triage visit, cervical dilation and fetal fibronectin test results.

As compared to those who did not have a fetal fibronectin test run, those with a positive test were 1.4 times (p= 0.004 95% CI 1.12, 1.76) times more likely to be admitted to the hospital after adjusting for multiple visits, group, maternal age, gestational age at triage visit, and cervical dilation.

As compared to those with cervical dilation greater than 1, those with dilation of less than or equal to 1 were 0.92 times more likely to be admitted to the hospital after adjusting for cohort, maternal age, gestational age at triage visit, and history of preterm delivery.

Table 26. Final Poisson regression model to predict risk of hospital admission for subjects after adjusting for multiple visits.

Variable	Beta	SE	pvalue	OR	95%CI
Intercept	0.27	0.13	0.04		
Group (reference 2000)	-0.02	0.02	0.33	0.98	0.94, 1.02
Maternal age	-0.001	0.002	0.56	0.999	0.995, 1.003
Gestational age at triage visit	0.001	0.003	0.84	1.00	0.99, 1.01
History of preterm delivery (ref yes)	-0.09	0.033	0.007	0.91	0.86, 0.98
Fetal fibronectin test					
Not run (reference)					
Negative	0.03	0.03	0.24	1.03	0.98, 1.02
Positive	0.34	0.12	0.004	1.40	1.12, 1.76
Cervical dilation (reference >1)	-0.08	0.02	0.003	0.92	0.87, 0.97

CHAPTER 5

DISCUSSION AND CONCLUSION

No association was seen between the exposures of interest, the 2000 and 2001 groups, and preterm delivery, which suggests this study failed to demonstrate a difference in preterm delivery after the availability of fetal fibronectin testing (OR= 0.92; 95% CI 0.68, 1.26) after adjusting for triage visits, previous preterm delivery, and maternal age. The failure of this study to demonstrate a significant reduction in preterm delivery, NICU admission, and hospital admission in this study may be largely attributable to limited power. The unexpected limited use of the fetal fibronectin assay during the first six months of availability minimized the potential for impact on patient care. Among the subjects eligible for fetal fibronectin testing in the 2001 cohort, only 47% (183/390) of subjects received fetal fibronectin testing at 36% of eligible visits (215/601), limiting the sample size receiving the test and potential impact on patient care. Although the use of the test did increase significantly (chi square for trend, $p < 0.001$) during the first six months of test use, the study period may have been too soon after test availability, or of insufficient duration to demonstrate meaningful differences. In addition, variability in physician preference, practice or cost considerations may have influenced test use and patient care decisions, limiting the efficacy of the test to reduce preterm birth, NICU admission, and use of hospital services. When the test became available, the implementation process took time, and there was a lack of protocols, policies

or consensus for use of the test and test results. The study findings may have been more profound with use of test on all “rule out preterm labor” patients, or all patients admitted to the hospital for preterm labor or more provider consensus regarding use of the test.

The lack of findings related to preterm delivery and NICU admission is comparable to previous studies using similar study designs. Joffe (Joffe et al., 1999) reported that 76% (251 of 330) of eligible patients had fetal fibronectin testing during the first 12 months of test availability as compared to 47% for our study. Similar to our findings, no difference was seen in gestational age at delivery (p=0.45), deliveries at less than 35 weeks gestation (p=0.17), or NICU admissions (p=0.53). Abenhaim and colleagues (2005) compared a historical cohort (n=116) and prospective cohort (n=116) of symptomatic patients between 24 and 34 weeks gestation after availability of the fetal fibronectin assay and also failed to demonstrate a difference in delivery prior to 37 weeks between the two cohorts (8.6% vs. 7.8%, NS). Early studies suggested fetal fibronectin testing could be an important biomarker to decrease future preterm delivery rates (Garite & Lockwood, 1966; Goldenberg et al., 1996a; Goldenberg et al., 1996b; Iams et al., 1995), however, this has not been seen, and the preterm birth rate actually increased to 12.7% in 2007 (PeriStats, 2009), as compared to rates before the availability of the fetal fibronectin assay.

This study demonstrated the predictive ability of the fetal fibronectin test was comparable to previous studies. Most studies suggested the principal utility of fetal fibronectin testing lies in the high negative predictive value for delivery

within 7 to 14 days with values of 90 to 99.5% (Foxman et al., 2004; Giles et al., 2000; Peaceman et al., 1997; Plaut et al., 2003; Swamy et al., 2005). The negative predictive value in this study (100%) for delivery within 14 days was higher than expected, however, the high negative predictive rate did not lead to a demonstrable decrease in preterm delivery or use of hospital based services. This study found no relation between risk of hospital admission and the exposure of interest, the two cohorts (OR= 0.98, p= 0.33, 95% CI 0.94, 1.02) after adjusting for multiple visits, maternal age, gestational age at triage visit, history of preterm delivery, cervical dilation, and fetal fibronectin test results. These results suggest the availability of the test did not reduce hospital admissions; however, lack of findings may be attributable to the limited use of the test and insufficient power to detect a significant difference.

The lack of findings regarding reduced hospital stay is consistent with several other studies. Plaut and colleagues (2003) found hospital stay was not significantly shorter with negative fetal fibronectin test results. A cost-analysis study in 2001 concluded use of the fetal fibronectin assay may be useful in decreasing admissions and costs if only used after decision to admit the patient to the hospital (Sullivan et al., 2001). Knowledge of fetal fibronectin result did not lead to significant reductions in length of initial hospital observation, hospital admission, or tocolysis or total health care related costs in a study by Grobman and colleagues in 2004.

The lack of findings related to hospital admission is inconsistent with several previous studies. The primary aim of the Joffe study (1999) was to

evaluate whether the fetal fibronectin assay would decrease hospital admissions. The authors demonstrated a decrease in the percent patients admitted for preterm labor (28.1%, 17.0%, p< 0.001), and decrease in mean length of stay per admission (2.0, 1.6, p< 0.001), however the sample included a full year each for the baseline cohort and test cohorts (n=243) and 76% received the test during the first 12 months of testing. Similarly, Lowe and colleagues (2004) investigated the effect of the rapid fetal fibronectin testing on length of hospital stay (n=97), and found a negative fetal fibronectin was associated with fewer admissions (p= 0.032) and a shorter length of stay (p= 0.008) in a university research setting. Abenhaim and colleagues (2005) also found a decrease in hospital admissions (24.1% vs. 12.1%, p= 0.03) and mean length of stay for preterm labor from 5.2 days to 0.6 days (p <0.001) after the availability of fetal fibronectin testing in Canada (n=116 tests) during a 20 week study interval. However, these studies were research studies conducted in academic research settings under more rigorous protocols, and consistent guidelines for use of the test. Although patient management may have been “at the discretion of the attending physician”, it is likely that university settings have more clinical consensus, consistent practice and patient management as compared to a community based hospital with non-employee, multiple provider groups with widely varied practice.

A history of preterm delivery is a predictor of subsequent preterm delivery (Behrman & Butler, 2007). The proportion of women with a history of preterm delivery in this study was 14.2% in 2000 and 13.1% in 2001 (p= 0.64) and consistent with literature based estimates among singleton pregnancies (Bloom

et al., 2001). In this study, among subjects having fetal fibronectin testing, those with a history of preterm delivery were 3.85 times (p=<0.001, 95% CI 2.49, 5.98) more likely to deliver preterm after adjusting for cohort, maternal age, and triage visits. This finding is comparable to previous estimates of a three to fourfold increase in recurrent preterm delivery, as compared to women without a history of preterm delivery (Bloom et al., 2001, Keifer & Vintzileos, 2008). Among those with positive fetal fibronectin testing in this study, 39% (7/18) had a history of preterm birth in a previous pregnancy.

The primary utility of the fetal fibronectin assay is the high negative predictive value, and a negative assay in a symptomatic woman may be used clinically to avoid unnecessary or expensive interventions such as hospital admission or glucocorticoid administration (Kiefer & Vintzileos, 2008; Lockwood et al., 2009; Yeast & Lu, 2007). However, other studies suggest fetal fibronectin may be cost effective only when clinicians are comfortable using the results to alter patient care (Lockwood et al., 2009). At the time of this study, it is likely the attending physicians were not comfortable or confident in the test, or in using test results to alter patient management. The most frequently cited clinical use of fetal fibronectin testing is to allow patient and physician reassurance with a negative test in a symptomatic patient. This should theoretically lead to decreased admissions and use of interventions or tocolytics, however, consistent demonstration of these findings remains elusive. In a review of patients who underwent fetal fibronectin testing (n=111) over a 19-month period between 2004 and 2006, one third of patients with negative fetal fibronectin were still managed

and treated for preterm labor, however, the management did not increase the length of gestation (Paláez, Fox, & Chasen, 2008).

Since the time of this study, subsequent studies have demonstrated that patient management should not be based upon fetal fibronectin test results alone, but rather be based upon test results and results of a combination of clinical factors including contraction activity, cervical length, infection, and patient history and characteristics (Behrman & Butler, 2007; Kiefer & Vintzileos, 2008; Yeast & Lu, 2007). Efforts to further enhance diagnostic accuracy in preterm labor have evolved, including the use of transvaginal sonography combined with fetal fibronectin testing, which has reduced the false positive diagnosis of labor (ACOG 2003; Behrman & Butler, 2007; Kiefer & Vintzileos, 2008; Leitich et al., 1999). A cervical measurement by transvaginal sonography of 30 mm or more suggests that preterm labor is unlikely in symptomatic women (Iams 2003) and a cervical length less than 30 millimeters and positive fetal fibronectin testing may identify women at very high risk of preterm birth (Gomez et al., 2005). Studies by Schmitz and colleagues (Schmitz, et al., 2006) and Gomez and colleagues (Gomez et al., 2005) have shown that utilizing both tests improves the screening process and specificity as compared to fetal fibronectin alone. Gomez and colleagues found improvement in the prediction of preterm delivery with 76% agreement ($p < 0.01$) between cervical length < 15 mm and positive fetal fibronectin (Gomez et al., 2005).

The findings of the current study confirmed the relation between change in cervical status and fibronectin test results. Among women with a positive test

with a corresponding cervical examination, 65% (n=11) were dilated greater than 1 centimeter as compared to 25% of women with a negative test (n=45). In the multivariable, repeated measures analysis, women with cervical dilation less than 1.0 centimeter were 0.74 times more likely to have a positive fetal fibronectin test after adjusting for gestational age at test and multiple tests.

Given the high correlation between cervical length and fetal fibronectin status, Kurtzman (2009) suggests the initial test for a symptomatic woman may be either fetal fibronectin or transvaginal ultrasound cervical length measurement, depending upon the resources of the institution, as the negative predictive value of each test is comparable. However, the positive predictive value of each test is limited. Whether the initial test is positive or negative, the predictive efficacy may be enhanced by the other test. Kurtzman further suggests that if one test is positive, the other test should be used, and the positive predictive value of the combined tests may be more than additive compared to each test alone (Kurtzman, 2008, 2009). The use of delivery probability profiles using the three “best” evidence-based risk factors to predict preterm delivery; fetal fibronectin, cervical length, and history of preterm birth, to generate survival curves for sub-populations may improve risk estimation in the future (Kurtzman, 2008, 2009).

Strengths

Selection of the study design for this study was influenced by a number of factors including availability of data, time sequence and duration of testing

implementation, time and cost constraints. The use of a retrospective cohort design was selected as the most robust design for the research questions, and allowed review of outcomes and services utilized before and after the test was implemented. The data for this study were retrieved from electronic and paper medical records sources, which allowed inclusion of all subject data for all subject visits for all baseline data and maternal and neonatal outcomes.

This study was able to address several limitations found in previous studies. Specifically, no previous studies included a sample of all subjects eligible for testing for six months prior to and after the availability of fetal fibronectin testing. This study included all patients meeting eligibility criteria for testing, and was not limited only to women having fetal fibronectin testing.

Prior to this study, the majority of fetal fibronectin research was performed by investigators in academic settings under more clearly defined, rigorous research protocols (Iams et al., 1995; Joffe et al., 1999; Garite & Lockwood, 1996; Giles et al., 2000; Goldenberg et al., 1998; Goldenberg et al., 2000a; Goldenberg et al., 2000b; Lockwood et al., 1991). Research protocols typically provide very specific guidelines for testing, interpretation of results, and patient management decisions. This study provides a historical record of implementation of a new diagnostic test, and a “real world” implementation experience, without a specific research protocol, in a large community hospital in non-academic setting with over 60 community obstetricians with increased subject, operator, physician, and practice variability. The study findings suggest implementation and optimal use of a new diagnostic test in a non-academic

clinical setting may require time and provider consensus, protocols or policies for use to attempt to replicate previous research findings in academic settings.

Limitations

This study has a number of limitations, which may have influenced study findings. The study interval was inclusive of the first six months of fetal fibronectin testing. Although the test use increased during the six-month interval, the slow implementation and limited use of the test likely provided an insufficient sample to address the study questions. In addition, the study may have been conducted too soon after test implementation to adequately address the study questions.

The study was limited in power to adequately address the research questions. The percent of subjects delivering prior to completion of 37 weeks gestation in 2000 was 33.9% (n=126) and 31.8% (n=124) in the 2001 cohort, which was not different (p=0.59). Using a critical significance level of 0.05, and a two-tailed test, the power to detect a significant difference in preterm birth was 9.5%. The cohorts consisted of 372 subjects in 2000 and 390 subjects in 2001. The percentage of subjects admitted was 7.5% for 2000 (28/372) and 11.5% (45/390) for 2001 which was not different (p= 0.06). Using the significance level of 0.05 and a two-tail test, the statistical power to detect a difference in admission was 46.7% and was diminished further by adjusting for the other confounders in the modeling.

Although there is a lack of reliable predictors for risk assessment for preterm birth, the inability to identify and control for several maternal factors known to be associated with preterm birth is a limitation in this study. Maternal risk factors unavailable or not measured included smoking, stress, marital status, socioeconomic status, body mass index, inflammation and infection (Behrman & Butler, 2007; Cunningham et al., 2001; Lockwood et al., 2009). Data regarding maternal infection was unavailable due to lack of guidelines for ascertainment, testing and treatment. Maternal infection is associated with preterm delivery and a positive fetal fibronectin test (Goldenberg et al, 1996b; Goldenberg et al., 1998).

The lack of a protocol or more standardized procedures or guidelines for test use, interpretation, and patient diagnosis and treatment likely led to significant variability among providers in this study. Physician preference and cost considerations may have influenced the use of the test and utilization of services and treatments. Physician caregiver comfort and confidence with the test may have been limited during the study interval. The lack of strict definitions for preterm labor and defined treatment algorithms may have limited the findings in this study. Clinically treated preterm labor often does not meet the classical definition for preterm labor (Behrman & Butler, 2007; Kiefer & Vintzileos, 2008; Sanchez-Ramos et al., 2009).

Data for this study were collected in a retrospective manner from electronic and paper medical records and may have been missing or inaccurate. Prenatal history data was collected from physician office records that were

placed in the hospital chart, and subject to missing or inaccurate data or non-standard definitions for variables of interest. The study may have also been limited by the prevalence of preterm labor signs and symptoms in this population, the proportion of subjects with outcomes of interest, and sparse data for various parameters.

The data used for this study was for 2000 and 2001 and may have decreased applicability or relevance to practice patterns and the use of fetal fibronectin today. Physician confidence and optimal use of the test results have evolved and become more refined since this study. Fetal fibronectin test results are typically used in conjunction with other factors including maternal history, contraction activity, cervical ultrasound, evaluation for infection, and other clinical or social risk factors.

Conclusions

Spontaneous preterm birth is a mutifactorial, diverse syndrome and identification of women who are or are not at risk for spontaneous preterm birth is challenging. Strategies to decrease preterm birth have been disappointing. Identification of risk factors fails to identify up to 70% of patients who will deliver preterm (Kurtzman 2009). Among the many challenges is the difficulty of an accurate clinical diagnosis of preterm labor, the current definition has up to a 50% false positive rate (Kiefer & Vintzileos, 2008). The diagnosis of preterm labor is imprecise, and many symptomatic patients will deliver at term (Kurtzman 2009). The accurate diagnosis of preterm labor is difficult because of the

variability in symptoms and signs, which can occur in healthy women who do not deliver preterm (Behrman & Butler, 2007). Nearly 50% of patients diagnosed with preterm labor and enrolled in non-treatment arms of randomized trials for tocolytic medications delivered at or near term (Sanchez-Ramos, et al., 2009).

Current therapies for preterm labor have limited efficacy, however, use of tocolytic medications may briefly prolong gestation to allow use of interventions shown to reduce neonatal morbidity and mortality. These interventions include antenatal transfer of the mother to a tertiary level center, antibiotic administration for group B streptococcus (GBS), and antenatal administration of glucocorticoids to the mother to hasten lung maturity in the fetus and reduce IVH and other sequelae (Gabbe, Niebyl, & Simpson, 2007).

Preterm birth, or birth before 37 weeks completed weeks gestation, is a major cause of pregnancy related morbidity and neonatal morbidity and mortality (March of Dimes 2005, PeriStats 2009), and the major obstetrical and neonatal problem in the developed world (Lockwood et al, 2009, PeriStats 2009). Recent research has focused on identification of potential biomarkers that may herald the onset of preterm labor or preterm premature rupture of membranes. The purpose of this investigation was to examine whether the availability of clinical fetal fibronectin testing had an impact on the gestational age at delivery, preterm delivery rate, neonatal intensive care unit admission rates, and differences in number of visits, admissions, or lengths of stay for treatment of preterm labor at a community tertiary-level hospital. The negative findings of this study are consistent with previous results suggesting fetal fibronectin may not directly

affect preterm delivery; it may however, be of value to identify women who are or are not at risk of preterm delivery.

Future Directions

The findings of this study suggest more clearly delineated protocols and treatment algorithms may be required when implementing new tests or biomarkers for identification of women at risk for preterm delivery in a non-research setting.

Further research is required to elucidate the complex etiology and challenges associated with identification and treatment of women at risk for preterm birth. Fetal fibronectin testing is commonly used in labor and delivery units, however, the conflicting results of previous studies suggests further research is needed to evaluate optimal and cost effective use of the assay in collaboration with other tests and risk factors in the clinical setting. Development and use predictive algorithms using survival curves or “delivery probability profiles” (Kurtzman, 2008) may lead to refined predictive ability in the future.

APPENDIX

A. 1

DATA COLLECTION FORMS (1 of 3)

Triage: Visit ____of_____
Clinical Use of the Fetal Fibronectin Assay at SMBHW

PI:_____
M Identifier:_____
H Identifier:_____
S Identifier _____
Physician Unique Identifier (code):_____

Perinatal Consult in triage or within 24 hours of admit NO YES

Date of Triage Visit:____/___/_____/_____ (dd/mm/yyyy/time)

Discharge Date: ____/____/_____/_____(dd/mm/yyyy/time)

EDC: _____ Gestational Age at Triage Visit:_____

Maternal Age:_____ Payor: (code) _____

Gravida_____ Para_____ Term_____
Preterm_____TAB_____SAB_____SB_____LB_____LC

Patient Admitted: No Yes

R/O PTL diagnosis: No Yes

Patient chief complaint: _____

Uterine Contractions: No Yes (describe number contractions per hour)
_____

Cervical Examination: No Yes ____/___/_____/_____ (dd/mm/yyyy/time)
Current cervical exam by sono: NO YES History short cervix by sono: NO YES
dilation _____ (cm) effacement _____ (cm) (or %_____) station _____ (-3 to +3)

FFN appropriate: No Yes

FFN collected: No Yes ____/___/_____/_____ (dd/mm/yyyy/time)

FFN Results: Negative Positive Not Done Time Noted: ____/___/_____/_____ (dd/mm/yyyy/time)

Tocolysis given: No Yes Time first dose: ____/___/_____/_____ (dd/mm/yyyy/time)

SQ terbutaline No Yes
Parenteral tocolysis (MgSO4) No Yes
Oral tocolysis No Yes
Ca++ channel blocker No Yes
NSAIDS (indocin, ibuprofen) No Yes

Antenatal Steroids Given: (this visit) No Yes

Hydration given: No Yes

Antibiotics given: No Yes

Other tests, treatments or medications given: No Yes
(describe)
_____
_____
_____
_____

Additional diagnoses, symptoms:
_____
_____
_____
Comments/Notes:
_____
_____

DATA COLLECTION FORMS (2 of 3)

Pregnancy Summary Form (one form for each qualifying patient)

PI:_____

M Identifier:_____

Inclusion Criteria:

1. Intrauterine singleton pregnancy
2. 24.0 – 34.9 weeks gestation
3. Triage visit to SMBHW for R/O PTL
4. No evidence of ruptured membranes
5. Cervix less than 3.0 cm dilated
6. No vaginal bleeding
7. No sexual intercourse, digital examination, or amniocentesis in prior 24 hours
8. Appropriate for clinical use of fetal fibronectin assay

Ethnicity:_____
Marital Status:_____

Delivery Date: ____/___/_____/_____ (dd/mm/yyyy/time)

Delivery admission Date: ____/___/_____/_____ (dd/mm/yyyy/time)

Delivery discharge Date: ____/___/_____/_____ (dd/mm/yyyy/time)

Gestational age at delivery _____.___ weeks (days)

Labor/delivery: (1) NSVD (2) low forceps (3) mid forceps (4) vacuum assisted (5) primary c/s in labor (6) primary c/s not in labor (7) repeat c/s in labor (8) repeat c/s not in labor

Labor: (1) spontaneous (2) Induced (3) Augmented (4) Not applicable

Reason for C-section

(1) dystocia/ftp
(2) fetal distress
(3) breech
(4) repeat C-section, not in labor
(5) repeat C-section, in labor
(6) infection

(7) preeclampsia
(8) other- describe_____
(9) not applicable

Total number of triage visits:(for R/O PTL) _____

Total number of admissions: (for PTL) _____

Total length of stay- pregnancy:(maternal)_____

Total cost all inpatient services: _____

Total cost all outpatient services:_____

Total cost: (inpatient plus outpatient)_____

DATA COLLECTION FORMS (3 of 3)

Infant Information

M identifier :_____

H identifier :_____

Infant status: (1) viable, well
(2) viable with compromise
(describe)_____
(3) demise (describe cause) _____

Gender of infant: M F

Birthweight:_____

Gestational age at birth_____

Neonatal ventilation: Yes No If yes, total hours _____

Fetal anomalies:(describe) _____

Survanta doses _____(number)

RDS Diagnosis No Yes
Oxygen at 36 wks No Yes
IVH grade _____ (number)

Hospitalization days:
Newborn (MIS) _____
Newborn (stepdown)_____
Newborn (NICU) _____

Total length of stay: _____Total costs: _____

Comments/notes:_____
_____
_____
_____

Appendix A. Table A1. Univariate associations with preterm delivery before and after the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

Preterm delivery <37weeks

	2000 (n=372)	2001 (n=390)
Preterm Delivery (n, %)	126 (33.9)	124 (31.8)
	OR (95% CI)	OR (95% CI)
Maternal age	1.01 (0.98, 1.05)	1.01 (0.97, 1.04)
Maternal age (categories)		
25 - 34 years (reference)	1.0	1.0
16 - 24	1.05 (0.55, 2.02)	1.06 (0.61, 1.84)
>= 35	1.31 (0.81, 2.10)	1.10 (0.66, 1.82)
Ethnicity		
White (reference)	1.0	1.0
Hispanic	0.87 (0.51, 1.48)	0.95 (0.54, 1.67)
African American	1.51 (0.65, 3.51)	0.52 (0.21, 1.26)
Asian	0.90 (0.45, 1.81)	0.52 (0.26, 1.04)
Ethnicity (White/all other)	0.98 (0.64, 1.51)	0.73 (0.47, 1.13)
Ethnicity (AfricanAm/all other)	0.64 (0.28, 1.45)	1.76 (0.74, 4.18)
Parity (nulliparous/multiparous)	1.63 (1.03, 2.59) *	1.14 (0.74, 1.75)
Previous preterm delivery (No/Yes)	3.95 (2.16, 7.24)***	4.04 (2.19, 7.44)***
Gestational age Triage V1	1.04 (0.97, 1.12)	0.96 (0.89, 1.03)
Gestational age Triage V1		
24.0 to 28.0 (reference)	1.0	1.0
28.1 to 32.0	0.91 (0.54, 1.53)	0.72 (0.42, 1.24)
32.1 to 34.6	1.22 (0.71, 2.11)	0.76 (0.44, 1.31)
Number Triage visits (1 versus > 1)	1.53 (0.98, 2.39)	1.54 (0.99, 2.40)

* p< .05, ** p< .01, ***p< .001

Appendix A. Table A2. Logistic regression models to predict preterm delivery before (2000) and after (2001) the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

variable	2000 Beta	SE	P	OR	95% CI	2001 Beta	SE	P	OR	95% CI
Intercept	-3.26	1.36	0.02	0.04		-008	1.39	0.79	0.68	
Maternal age (one year increase)	-0.01	0.02	0.55	0.99	(0.95, 1.03)	-0.002	0.93	0.93	1.002	(0.96, 1.04)
Ethnicity (reference Caucasian)	-0.06	0.24	0.81	0.95	(0.59, 1.51)	-0.40	0.24	0.09	0.67	(0.42, 1.07)
Parity (reference nulliparous)	0.14	0.27	0.59	1.15	(0.69, 1.94)	0.19	0.25	0.45	0.83	(0.50, 1.36)
Previous preterm delivery (no)	1.32	0.33	<0.001	3.73	(1.94, 7.19)	1.49	0.34	0.00	4.42	(2.28, 8.55)
Gestational age Triage visit 1	0.09	0.04	0.04	1.09	(1.01, 1.18)	-0.02	0.04	0.68	0.98	(0.91, 1.07)
Triage visits (1)	0.44	0.25	0.08	1.55	(0.94, 2.56)	0.35	0.25	0.15	1.42	(0.88, 2.31)

Appendix A Table A3. Final logistic regression model to predict preterm delivery before (2000) the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

2000

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-3.31	1.24	0.007	0.04	
Previous preterm delivery (no)	1.35	0.32	<0.001	3.86	2.08, 7.14
Gestational age Triage visit 1	0.08	0.04	0.06	1.08	0.99, 1.17
Triage visits (1)	0.45	0.25	0.08	1.56	0.96, 2.55

Appendix A. Table A4. Final logistic regression model to predict preterm delivery after (2001) the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

2001

Variable	Beta	SE	pvalue	OR	95% CI
Intercept	-0.87	1.24	0.48		
Previous preterm delivery (no)	1.37	0.32	<0.001	3.92	2.12, 7.27
Gestational age triage visit 1	-0.007	0.04	0.86	0.99	0.92, 1.07
Triage visits (1)	0.38	0.24	0.12	1.46	0.91, 2.34

Appendix A Table A5. Univariable associations with NICU Admission before and after the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

	2000 (n=372)	2001 (n=390)
	(n,%)	*(n,%)*
NICU/stepdown admissions	36 (9.7)	35 (9.0)
	OR (95% CI)	OR (95% CI)
Gestational Age at Delivery	0.47 (0.38, 0.59)*	0.48 (0.39, 0.60)*
Maternal age at Triage Visit 1	0.99 (0.94, 1.05)	1.04 (0.99, 1.11)
Ethnicity		
White (reference)	1.0	1.0
Hispanic	0.74 (0.30, 1.79)	1.0 (0.41, 2.45)
African American	0.76 (0.17, 3.44)	0.93 (0.26, 3.31)
Asian	0.64 (0.18, 2.24)	0.17 (0.02, 1.27)
Parity (nulliparous)	0.86 (0.42, 1.73)	1.22 (0.59, 2.49)
Previous preterm delivery (reference no)	2.52 (1.14, 5.56)*	2.58 (1.13, 5.88)*
Gestational age Triage V1	1.03 (0.92, 1.16)	0.99 (0.88, 1.11)
Number Triage visits (reference 1 visit)	0.91 (0.44, 1.88)	0.56 (025, 1.28)

* p< .05, ** p< .01, ***p< .001

Appendix A. Table A6. Univariable and gestational age at delivery adjusted measures of association with NICU admission before and after the availability of fetal fibronectin testing among women with signs and symptoms of preterm labor.

	2000 (n=372)		2001 (n=390)	
	(n,%)		*(n,%)*	
NICU/stepdown admissions	36 (9.7)		35 (9.0)	
	OR (95% CI)	Gest Age Adjusted OR (95% CI)	OR (95% CI)	Gest Age Adjusted OR (95% CI)
White (reference)	1.0	1.0	1.0	1.0
Hispanic	0.74 (0.30, 1.79)	0.88 (0.32, 2.41)	1.0 (0.41, 2.45)	0.57 (0.16, 1.92)
African American	0.76 (0.17, 3.44)	0.54 (0.09, 3.37)	0.93 (0.26, 3.31)	1.46 (0.09, 3.37)
Asian	0.64 (0.18, 2.24)	0.62 (0.16, 2.42)	0.17 (0.02, 1.27)	0.25 (0.16, 2.42)
Nulliparous	0.86 (0.42, 1.73)	0.63 (0.28, 1.46)	1.22 (0.59, 2.49)	1.38 (0.59, 3.24)
Previous preterm delivery (no)	2.52 (1.14, 5.56)	0.48 (0.39, 0.60)	2.58 (1.13, 5.88)*	0.91 (0.32, 2.54)
Gestational age Triage V1	1.03 (0.92, 1.16)	1.04 (0.91, 1.18)	0.99 (0.88, 1.11)	1.09 (0.94, 1.25)
Number Triage visits (1)	0.91 (0.44, 1.88)	0.58 (0.25, 1.36)	0.56 (0.25, 1.28)	0.47 (0.19, 1.19)

Appendix A. Table A7. Key Publications Using Fetal Fibronectin Testing to Predict Preterm Delivery

Authors, Year	Research Objective	Study Design Sample Size	Study Population Inclusion/exclusion/ Sampling Intervention Treatment	Outcome Measures	Comments/Conclusions/Statistical modeling NPV PPV Sens Spec p value OR/RR
Lockwood, Senyei, Dische, et.al. 1991	Presence of fetal fibronectin and risk of preterm birth	Prospective cohort N=117 (intact membranes) N=65 PPROM Normal pregnancy n=163 83% Positive FFN 19% Negative FFN	Uncomplicated pregnancies, no symptoms Measured cervical/vaginal, maternal plasma FFN Quantitative assay	Delivery at < 37 wks	NPV PPV Sens Spec p value OR/RR 81% 83% 82% 83% <0.01 n/a PTB and FFN status and EGA at delivery, days to delivery, birthweight all significant p=0.0001 Conclusion: FFN effective at predicting preterm birth at < 37 weeks FFN identifies a subgroup of women at risk for preterm delivery
Lockwood, Wein, Lapinski, et.al.1993	Serial assessment of cervical and vaginal FFN to predict preterm delivery	Prospective cohort N=429 Spontaneous PTB=11%	Symptom free, inner-city, general obstetrical population Quantitative assay	Cervical FFN > 60ng/ml Vaginal FFN> 50ng/ml Delivery <37 weeks	NPV PPV Sens Spec p value OR/RR 95% 25% 73% 72% 95% 30% 68% 80% Cervical FFN predicted PTD OR=8.9 Vaginal FFN predicted PTD OR=6.0 FFN in cervicovaginal secretions has potential as screening test for PTD

Appendix A. Table A7 continued

Nageotte, Casal, Senyei 1994	Evaluate FFN as a screening test for preterm delivery	Prospective cohort N=87 Spontaneous PTB=31%	Asymptomatc, increased risk PTB Weekly sampling until 34 weeks Quantitative assay	Delivery <37 weeks Delivery < 34 weeks	NPV PPV Sens Spec p value OR/RR 93.9% 46.3% 92.6% 51.7% 97.8% 92.3%
Iams, Casal, McGregor, et.al. 1995	Assess utility of cervical vaginal expression of FFN in diagnosis of preterm labor	Prospective cohort N=192 Spontaneous PTB=32.3%	Symptomatic 24 to 34 weeks Quantitative assay	Delivery <37 weeks Delivery < 7 days Delivery < 14 days Delivery < 21 days	NPV PPV Sens Spec p value OR/RR 76% 60% 44% 86% p=0.000 OR=4.8 99% 29% 93% 82% p=0.000 OR=59.3 95% 40% 69% 84% p=0.000 OR=11.6 90% 58% 65% 88% p=0.000 OR=13.0 FFN sensitive and specific indicator of delivery within 7 days. Superior to contraction frequency and cervical dilation.
Bartnicki, Casal, Kreaden, et.al. 1996	Evaluate vaginal FFN expression and risk of preterm delivery and low birth weight infant	Prospective cohort n=112 Spontaneous PTB=35.7%	Symptomatic Vaginal secretions 22- 35 weeks Quantitative assay	Delivery <37 weeks Delivery of infant < 1500 grams birth weight	NPV PPV Sens Spec p value OR/RR 83.3% 79.4% 67.5% 90.3% p<0.0001 OR=19.3 32.4% positive FFN versus 2.5% negative FFN p<0.0001 FFN is independent risk factor for prediction of preterm delivery and delivery of low birth weight infant

Appendix A. Table A7 continued

Goldenberg Mercer, Meis, et.al. 1996	Evaluate the presence of FFN in cervix and vaginal secretions as screening test for spontaneous preterm birth	Multi-center Prospective cohort N=2929	Asymptomatic Screened every 2 weeks from 22-24 to 30 weeks Quantitative assay	Delivery <37 weeks	Presence of FFN with increasing gestational age PPV= 13-36%, Sensitivity=63%, Specificity =96-98% RR=59 Positive cervical or vaginal FFN at 22-24 weeks predicted more than half of spontaneous preterm births at <28 weeks
Goldenberg Thom, Moawad et.al. 1996	Relationship between vaginal and upper genital tract infection and cervicovaginal FFN	Multi-center Prospective cohort N=2899	Asymptomatic Screened every 2 weeks from 23-24 weeks to 30 weeks Quantitative assay		Women with bacterial vaginosis more likely to have positive FFN test OR=16.4 Women with positive FFN who delivery at <32 weeks (p=0.02) had histological evidence of chorioamnionitis Evidence to support the linkage between genital tract infection and presence of FFN
Peaceman, Andrews, Thorp, et.al. 1997	Determine whether presence of FFN in symptomatic patients predicts preterm delivery	Multi-center Prospective cohort N=763 MDs blinded to results	Symptomatic 24 to 34+6 weeks FFN positive =20% Quantitative assay	Delivery <7 days Delivery < 14 days Delivery <37 weeks	NPV=99.5% RR=25.9 NPV=99.2% RR=20.4 NPV= 84.5% RR=2.9 Multiple logistic regression predicting delivery within 7 days, presence FFN (OR=48.8) previous preterm birth (OR=8.3) and tocolysis (OR=4.1) High NPV supports less intervention for patients with negative FFN

Appendix A. Table A7 continued

Goldenberg Mercer, Iams, et.al. 1997	Determine how various patterns of FFN positive patients from 24-30 weeks predicts subsequent test results and spontaneous preterm delivery	Multi-center Prospective cohort N=2929	Asymptomatic Sampled at 24,26,28, 30 weeks Quantitative assay	Predict whether next FFN test is positive or negative Predict percent with spontaneous preterm delivery within 4 weeks after FFN	Women with previous negative test had 3% chance of subsequent positive test If last test positive, 29% will have the next test positive Higher number of positive tests in individual patient, greater risk of spontaneous preterm delivery
Benattar, Taieb, Fernandez, et.al. 1997	Evaluate value of rapid FFN in prognosis for preterm labor	Prospective cohort N=124	Symptomatic 24 to 36+6 weeks FFN positive=19 Rapid assay	Delivery <7 days Delivery <14 days Delivery < 21 days Delivery < 32 weeks Delivery < 37 weeks	NPV PPV Sens Spec 99% 42% 89% 90% 95% 57% 69% 93% 81% 58% 46% 91% 97% 55% 73% 91% 85% 50% 36% 91% Rapid assay results compared favorably to quantitative assay

Appendix A. Table A7 continued

Lukes, Eucker, Pahel-Short, et.al. 1997	FFN used to identify patients at risk for preterm delivery	Multi-center Prospective cohort N=763 Results not available to MDs	Symptomatic 24 to 36+6 FFN positive =20% Quantitative assay	Use of variables to predict positive FFN Cervical dilation Vaginal bleeding Sexual activity Cervical exam	Five significant variables= cervical dilation, sexual activity within 24 hours, vaginal bleeding, cervical exam within 24 hours, uterine contraction activity. Cervical manipulation or cervical dilation predicts positive FFN assay. Results may explain some false-positive FFN assays.
Coleman, McCowan, Pattison, et.al. 1998	Evaluate bedside FFN test and evaluate specimens collected with and without speculum	Prospective cohort N=121 Results not available to MDs	Symptomatic 24 to 36+6 weeks FFN positive =22% Bedside assay	Delivery <10 days	NPV PPV Sens Spec 94% 41% 65% 85% positive LR=4.3 FFN positive and cervical dilation >=1 independently predicted delivery within 10 days
Joffe, Jacques, Bemis-Heys, et.al. 1999	Determine whether use of FFN assay would decrease admissions for diagnosis and treatment of preterm labor	Prospective cohort using baseline 12 month historical cohort N=243	Symptomatic 24 to 34.9 weeks Results available in 24 to 34.9 hours	Delivery at < 35 weeks Admissions for preterm labor LOS Tocolytics Neonatal outcome	No difference between baseline and study groups. Admissions for preterm labor baseline 28.1% versus study 17.0 (p<0.001) Use of FFN assay reduced admission for preterm labor, reduced length of stay in hospital and prescriptions for tocolytic medications No impact on neonatal outcomes

Appendix A. Table A7 continued

Giles, Bisits, Knox, et.al. 2000	Determine whether bedside testing affected costs and maternal transfers	Multi-center Prospective cohort N=151	Symptomatic 24 to 34+6 FFN positive =45 Australia	Delivery at <37 weeks Maternal transfers	NPV 93.4% Use of FFN led to 90% decrease in maternal transfers.
Lopez, Francis, Garite, et.al. 2000	Examine whether FFN more useful to predict preterm delivery in clinical practice than in prospective blinded studies	Retrospective cohort N=85	Patients with FFN results in past 2 years	Delivery <7 days	NPV PPV sens spec 98% 40% 89% 84% PPV ($p<0.002$) better in actual clinical practice than in previous prospective studies at predicting delivery within 7 days
Sullivan, HueppchenSatin 2001	Cost-effectiveness of bedside FFN testing	Cost analysis modeling Retrospective 11 month interval	Symptomatic	Admissions for preterm labor Costs	Utilizing assay on all PTL patients may be cost effective in reducing admissions and costs if used AFTER decision to admit

Appendix A. Table A7 continued

Lu, Goldenberg Cliver, et.al. 2001	Vaginal fetal fibronectin levels and spontaneous preterm birth in symptomatic women	Nested Quantitative FFN values from two prospective multicenter trials N=725 + 563	Symptomatic and asymptomatic 24 to 34+6 weeks Quantitative assay	Delivery < 35 wks Delivery < 37 wks Delivery < 7 days Delivery < 14 days Delivery < 21 days	Trial (40-100vs<40ng/ml) (<40 vs >100ng/ml) RR (Trial A) RR(Trial B) RR (Trial A) RR (Trial B) 3.2 1.7 8.9 6.8 1.8 2.3 4.0 3.0 8.3 5.7 48.1 21.5 5.5 2.7 41.2 14.1 2.1 3.2 8.0 10.0 Increasing FFN values associated with progressive increase in risk of preterm delivery. Suggests re-evaluate cutoff value of 50ng/ml.

Appendix A. Table A7 continued

Rinehart, Terrone, Isler, et.al. 2001	Pregnancy outcome in women with preterm labor without cervical change according to FFN status	Prospective cohort N=235 Positive FFN=20%	Symptomatic, no cervical change 24-34 weeks	Delivery < 7 days Delivery <28 wks Delivery < 34 wks Delivery < 37 wks Clinical utility	NPV PPV Sens Spec 94 33 57 85 100 36 100 87 90 38 50 85 65 71 35 90 Patients with symptoms but no cervical change with negative FFN less likely to delivery preterm
Goldenberg, Iams, Das, et.al. 2002	Elucidate pathogenesis of preterm birth using traditional risk factors and cervical length and FFN	Prospective cohort N=3076 Multi-center	Asymptomatic Serial collections, FFN and cervical length	Delivery <35 wks	Short cervix predicts a subsequent positive FFN and positive FFN predicts subsequent short cervix.
Plaut, Smith, Kennedy 2003	Impact of rapid FFN on treatment of preterm labor symptoms	Prospective, Randomized Multicenter N=108 Positive FFN n=10	Symptomatic 24 to 34+6 weeks FFN results known versus unknown	Delivery < 14 days Length of hospital stay	NPV PPV Sens Spec 98 10 33 91 Prevalence=2.8% Hospital stay not significantly shorter for negative results unknown versus known

Appendix A. Table A7 continued

Foxman, Jarolim 2004	Use of FFN test in decisions to admit for preterm labor	Prospective cohort Survey to MD with test requisition re: intent to admit, treat N=175 Singletons n=152	Symptomatic 24 to 34 weeks Rapid assay First FFN only FFN Positive =22%	Delivery < 7 days + clinical data Delivery < 7days + survey	NPV PPV Sens Spec 99 19 86 81 98 14 67 78 Supports FFN reduces hospital stay for admits for preterm labor
Stevens, Chauhan, Magann 2004	Examine the relationship between bacterial vaginosis, FFN, preterm labor and preterm birth	Prospective cohort N=185	Symptomatic 24 to 34 weeks Collection FFN and bacterial vaginosis (BV) specimens	4 groups BV FFN A pos pos B neg pos C pos neg D neg neg Time test to delivery Delivery <32 wks	Time from test to delivery shorter for Group A and B versus C and D ($p<.05$ and $p<.001$) Increased in Group B (26%) versus A (9%) C(2%) D (5%) ($p<.009$)

Appendix A. Table A7 continued

Grobman, Welshman, Calhoun 2004	Examine whether FFN results affect patient treatment and costs	Prospective, randomized N=100 Results known versus unknown	Symptomatic 24 to 34 weeks Singletons Rapid assay	Length observation Hospital admissions Tocolysis Work cessation Total costs	Results known vs unknown 4 vs 3 hrs (NS) 28% vs 26% (NS) 18% vs 16% (NS) 27% vs 26% (NS) (NS)
Lowe, Zimmerman, Hansen 2004	FFN effect on length of stay, and preterm labor interventions	Prospective, randomized to FFN versus no FFN N=97 MDs not blinded	Symptomatic 23 to 34 wks Rapid assay	Admissions Hospital length of stay Use of PTL interventions	Negative FFN versus Positive FFN Admissions p=0.032 Length of stay p=.008 Interventions NS Negative FFN associated with fewer admissions and shorter length of stay.

Appendix A. Table A7 continued

Abenhaim, Morin, Benjamin 2005	Examine how the availability of FFN affects utilization of hospital resources Canada	Prospective cohort comparison with historical cohort 20 weeks study interval N=116+116	Symptomatic 24 to 34 weeks Rapid assay	FFN vs historical Admits Preterm delivery <37 wks Mean length of stay Costs Hospital costs	FFN vs historical 12.1% vs 24.1% (p=0.03) 7.8% vs 8.6% (NS) 0.6 vs 5.2 days (p<0.0001) FFN testing associated with fewer admits, shorter mean length of stay and decreased hospital costs
Gomez, Romero, Medina, et.al. 2005	Cervical length and vaginal FFN to predict preterm delivery among women with uterine contraction activity Chile	Prospective cohort N=215	Symptomatic 22 to 35 wks Cervical length and FFN collected Rapid assay Spontaneous PTB <35 weeks =20%	Delivery < 48 hours Delivery < 7 days Delivery < 14 days Delivery < 32 wks Delivery < 35 wks	Prevalence 7.9% 13.0% 15.8% 8.9% 15.8 Admit to delivery interval Kaplan Meier log rank test p<.0001 Cervical length predicts preterm delivery and FFN is associated with spontaneous preterm delivery

Appendix A. Table A7 continued

Musaad, Melson, Boswell 2005	Impact of FFN on diagnosis, length of stay, costs, and management among women with preterm labor New Zealand	Prospective cohort versus historical cohort controls N=30+ 30	Symptomatic 24 to 34 wks Rapid assay	Overall management costs Length of stay Hospital costs	Controls vs FFN NS "trend" decreased in FFN group (p=0.082) NS Patient management expenditures not reduced with FFN
Tekesin, Wallweiner Schmidt 2005	Evaluate clinical risk factors, FFN and cervical characteristics to predict preterm delivery Germany	Prospective cohort N=117 Cervical ultrasound and FFN	Symptomatic 24 to 34 wks Rapid assay	Delivery < 34 wks Delivery < 37 wks Delivery < 34 wks Delivery < 37 wks Delivery < 37 wks	Positive FFN OR=13.4 (p=0.003) Positive FFN OR=17.3 (p<0.001) Low gray scale cervix OR=6.3 (p=0.02) Low gray scale cervix OR=7.1 p=0.003 Combined parameters Low gray and negative FFN RR=10.3 Normal gray and positive FFN RR=18.1 Low gray and positive FFN RR=24.8 Combined tests improves diagnostic efficiency

Appendix A. Table A7 continued

Tekesin, Marek, Hellmeyer, et.al. 2005	Effect of FFN by rapid assay to predict preterm delivery Germany	Prospective cohort N=170	Symptomatic 24 to 34 wks Rapid assay	Mean gestational age at delivery Admit to delivery time Delivery < 7 days Delivery < 14 days Delivery <21 days	Positive FFN vs Negative FFN 35.71 weeks 38.63 weeks (p<.001) 36.1 days 63.4 days (p<.001) NPV PPV Sens Spec 98.4 19.6 81.8 76.7 98.4 30.4 87.5 79.2 96 37 77.3 80.4
Swamy, Simhan, Gammill, et.al. 2005	Clinical utility of FFN for predicting preterm birth	Prospective cohort N=404 Clinical pathway protocol used for decisions	Symptomatic 22 to 34 wks 11.4% positive FFN	Pos vs neg FFN Delivery < 7 days Delivery < 14 days Delivery < 32 wks Delivery < 37 wks Interventio ns for PTL	RR NPV PPV Sens Spec 22 98 30 67 92 22 12.3 5.1 (p<0.01)

Appendix A. Table A7 continued

Tsoi, Akmal, Jeffery, Nicolaides 2006	FFN and cervical length to predict preterm delivery South Africa	Prospective cohort N=195 Cervical length plus FFN MDs blinded	Syptomatic 24 to 34 wks	Delivery < 7 days	Cervix <15mm >15mm FFN pos FFN neg 51.4% 0.6% 21.2% 0.9% Significant association with cervical length and positive FFN (p=0.003) Logistic regression=delivery < 7 days, only positive predictor =cervical length. Other variables NS include: ethnicity, maternal age, gestational age, BMI, parity, history preterm delivery, cigarette smoking, tocolysis)

FFN=fetal fibronectin
Sens=sensitivity
Spec=specificity
NPV=negative predictive value
PPV=positive predictive value
PTB=preterm birth
EGA=estimated gestational age
PPROM=preterm premature rupture of membranes
PTD=preterm delivery
MD= physician
LOS=length of stay
BMI= body mass index
NS=not statistically significant
OR= odds ratio
RR=relative risk
LR=likelihood ratio

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