Laboratory Medicine Practice Guidelines for the Evaluation of the High-Risk Pregnancy

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Although there are a number of medical conditions that can affect the pregnant patient, these laboratory medicine guidelines review two high-risk pregnancy topics: (1) preterm birth and (2) fetal lung maturity.

Clinicians commonly classify pregnancies as low- and high-risk. Many causes contribute to the high-risk classification (see Table 1).

Table 1. High-risk pregnancies

Preterm Birth
Premature Rupture of Membranes
Twins and higher multiples
Isoimmunization Disease
Liver Disease
Pre-eclampsia (including HELLP)
Fetal anomalies
Infections (e.g. Group B streptococcus, HIV)
Maternal conditions (e.g. Graves)

Preterm Birth

Normal human gestations are approximately 40 weeks in duration. Preterm birth is delivery of the infant prior to 37 weeks' gestation. Those births before 32 weeks' are classified as very preterm birth. Newborns can also be classified by birth weight. Any infant <2500 g is classified as low birth weight (LBW) and those <1500 g are very low birth weight (VLBW). Preterm birth and LBW are the most common of the high-risk pregnancies.[1] Although from 1981 to 2000, the incidence of very preterm birth in the U.S. has been constant at 1.9 %, the incidence of preterm birth has increased from 9.4 to 11.6%.[1]

A variety of obstetrical and maternal conditions precede preterm birth, Table 2. Some of these conditions are causative and others are merely associations.

Table 2. Conditions associated with preterm birth

Obstetical	*Maternal*
Preterm Labor	Previous preterm birth
Preterm ruptured membranes	Diabetes
Pre-eclampsia	Asthma
Abruptio placenta	Drug abuse
Multiple gestation	Pyelonephritis
Placenta previa	Maternal race (higher in African Americans)

Fetal growth retardation	Poor nutrition
Excessive or inadequate amniotic fluid volume	Low pre-pregnancy weight
Fetal anomalies	Inadequate prenatal care
Amnionitis	Strenuous work
Incompetent cervix	High personal stress
	Anemia
	Tobacco use
	Infections

Preterm birth is categorized as spontaneous or indicated. Spontaneous preterm birth is more frequent, accounting for about ¾ of the cases, and occurs unplanned. The causes of spontaneous preterm birth include preterm labor, preterm premature rupture of membranes, amnionitis, and incompetent cervix. In ¼ of preterm birth cases the mother or fetus has a disorder that improves following delivery, for example pre-eclampsia or fetal distress. Early delivery in these cases is apt to improve both maternal and fetal outcomes. The clinician may therefore elect an early delivery. These preterm births are therefore indicated.

Even though the preterm birth rate has worsened, the infant morbidity and mortality rate for the preterm birth has improved. In 1980 the infant mortality rate in the United States was 12.6 per 1,000 live births. This declined to 6.9 per 1,000 live births in

2000.[2] Morbidity following preterm birth includes respiratory distress syndrome (RDS), bronchopulmonary dysplasia, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, and sepsis. Most preterm infants have extended hospital stays.

Tests for predicting preterm birth

Several tests have been advocated to predict preterm birth, including fetal fibronectin (fFN), cervical length by ultrasound, salivary estriol (Sal-Est), alkaline phosphatase, and maternal serum alpha-fetoprotein, and granulocyte colony stimulating formation.

Fetal fibronectin (fFN)

Fibronectin is adhesive glycoprotein that cross-links collagen to bind cells together. The fetal form has a unique epitope. Labor increases fFN in cervical and vaginal secretions. The specimen is obtained by collecting vaginal secretions in a specially designed Dacron swab. When fully saturated, the swab contains approximately 150 µL of secretions. fFN is measured by immunoassay; vaginal secretion fFN concentrations less than 50 ng/mL indicate that delivery is not imminent. Amniotic fluid is rich in fFN, therefore the test cannot be used in women with ruptured membranes. The FDA has approved fFN for the diagnosis of impending premature delivery in symptomatic women who are 24.0 to 34.9 weeks' gestation. For asymptomatic women who are 22 to 30.9 weeks' gestation, fFN is FDA approved for predicting the risk of preterm delivery. In this

group, the positive predictive value is a low 13%, but the negative predictive value is high at 99.5%.[3]

Half of mothers thought to be in preterm labor deliver at term without treatment. Without fFN testing, 20% of those sent home, deliver preterm. For predicting delivery within 7 days, in symptomatic women, studies[4, 5, 6, 7] have determined the sensitivity to be 57-93% and specificity to be 73-92% in women 24 to 34.9 weeks' gestation. The positive predictive value has varied from 9 to 29%, whereas the negative predictive value is much higher at 97-99.6%.

Recommendation: Use of fFN to veto the decision to admit a symptomatic patient to the hospital who is thought to be 24.0 to 34.9 weeks' gestation is cost effective.

Using fFN as a test to overrule the medical decision to admit a suspected preterm labor patient to the hospital appears to be cost-effective.[8] The baseline costs were estimated in women without the use of fFN. If fFN is used in women with mild preterm labor symptoms, more than twice as many would be admitted to the hospital, nearly doubling the cost. When used to exclude admissions in women with more significant preterm labor symptoms, fFN would decrease costs by about 18%. Thus, proper use of fFN is necessary to prevent unnecessary admissions and increasing health care costs.

Recommendation: although some studies report that fFN might be useful in predicting which women could have labor induced therapeutically, more outcome studies are needed

to determine the cost-benefit of this use.

Use of fFN has been proposed at term (38 to 42 weeks' gestation) to predict probability that delivery can be induced (reviewed in reference *9*). Most clinicians rely on the Bishop score[10] or cervical dilatation[11] for this assessment.

Salivary Estriol (Sal-Est)

Esteriol is a steroid hormone made by placenta from 16α-hydroxyl dehydroepiandosterone sulfate (16α-OH DHEA-S). This intermediate requires functioning fetal liver and adrenal glands. Esteriol is excreted in milligram amounts per day and rises throughout pregnancy. Salivary estriol reflects unbound, unconjugated serum estriol and is approximately 1.00 ng/mL at 30 weeks and 3.00 ng/mL at term. There is a surge in salivary esteriol about 5 weeks prior to delivery.[12] Salivary estriol is "still under assessment and should not be used outside research protocols."[13]

Recommendation: there is insufficient evidence to recommend the routine use of salivary estriol during pregnancy.

Predicting Spontaneous Preterm Birth

A large multicenter trial[14] termed the Preterm Prediction Study was conducted to identify a population at risk for preterm birth. Twenty-eight biologic markers were included. The study subjects were asymptomatic at 23-24 weeks' gestation. The outcomes were preterm delivery at <32 and <35 weeks' gestation.

Table 3. Predictors of preterm birth <35 wks*

Predictor	*Odds Ratio*
Fetal Fibronectin (>50 ng/mL)	6.6
Alkaline phosphatase (>90th percentile)	4.0
History of preterm birth	4.0
Cervical length (≤25 mm)	3.9
Maternal serum alpha-fetoprotein (>90th percentile)	3.9
Granulocyte CSF (>75th percentile)	3.1

*From reference *14*.

Recommendation: Preterm birth interventions are not effective in asymptomatic women, therefore tests, such as fFN and salivary estriol, that predict preterm birth in this group are not useful outside of the research setting.

Fetal Lung Maturity

Neonatal Respiratory Distress Syndrome (RDS) is a common disease of preterm infants and infants with delayed maturation, such as those born to poorly controlled diabetic mothers. This disorder is caused by a deficiency of surfactant. Treatment has improved dramatically and requires increased oxygen and mechanical ventilation. Treating the newborn with exogenous surfactant at birth can often ameliorate the symptoms.

The lungs make surfactant in the form of lamellar bodies (LB) inside Type II pneumocytes. These hydrophobic structures are 1-5 microns in diameter[15] and contain surface tension reducing phospholipids and three specific proteins, SP-A, B, C, and D.[16,17] The LB are excreted by exocytosis, and in the aerated lung, unravel to coat the air surface interface. Production starts as early as 28 weeks gestation, but there is a surge in production at about 36 weeks for most fetuses. The newborn lung contains about 100 times more surfactant per lung volume than the adult lung.

The phospholipid content of LB is mostly lecithin (phosphatidylcholine [PC]), phosphatidylinosital (PI), phosphatidylglycerol (PG), and phosphatidylethanolamine (PE), but little, if any, sphingomyelin (S). Low PC concentrations are present in amniotic fluid up to 36 weeks' gestation, when production surges. PG production starts at this time in most normal pregnancies.[18]

Testing for FLM has declined over the past 10 years. Surfactant therapy and clinical adherence to obstetrical guidelines have lessened demand. The clinician uses FLM results to assess whether best infant survival will be achieved in utero or following an early

delivery. Knowing that fetal lung is producing adequate surfactant sways the decision toward delivery. The clinician can delay delivery by using tocolytic drugs such as ritodrine, can accelerate fetal surfactant production by administering steroids to the mother and delivering after 3 days, and can enhance labor and early delivery with the use of pitocin.

FLM testing is not indicated in normal pregnancies if the gestational age is accurately known to be at least 36 weeks.[19] The best evidence for determining fetal maturation is an early positive pregnancy test at least 36 weeks in the past. Fetal heart tones for 20 weeks or ultrasonographic evidence of a fetal heartbeat for 30 weeks, are also good indicators of a fetus that is old enough to have achieved pulmonary maturity. Also useful is ultrasound dating at 6 to 11 weeks' gestation that supports a pregnancy of at least 39 weeks, or measurements at 12-20 weeks' gestation that confirm a pregnancy of at least 39 weeks.

An ideal FLM test would be an imaging test available at the bedside. Such a test does not exist currently. All valid tests require analysis of amniotic fluid. This is best collected by amniocentesis even in the presence of ruptured membranes. The method should be available in most laboratories, not affected by blood or meconium, with results available rapidly at any time. False mature results have more dire medical consequences than do false immature results, because the former may tip the scales toward an unwarranted early delivery decision.

Tests for predicting Fetal Lung Maturity

Available tests for predicting fetal lung maturity are listed in Table 4.

Table 4. Use of fetal lung maturity testing methods (2002)*

Method	Source	Number of Laboratories [a]
Surfactant/albumin ratio (TDx FLM II)	Abbott Laboratories	462
Phosphatidylglycerol (AmnioStat-FLM)	Irving Scientific	447
Lecithin/sphingomyelin ratio	Helena Laboratories, and "laboratory developed test"	138
Phosphatidylglycerol (1 dimensional TLC)	"laboratory developed test"	92
Phosphatidylglycerol (2 dimensional TLC)	"laboratory developed test"	18
Lamellar body counts (LBC)	"laboratory developed test"	59 [b]
Foam Stability	"laboratory developed test"	Fewer than 50 [c]
Fluorescence polarization (NBD-PC), FPol	"laboratory developed test"	9

* Modified from Handbook of Clinical Laboratory Testing during Pregnancy, Gronowski AM, Ed., Humana Press, New York, 2004, page 58.

[a] Data from reference *20*, unless stated otherwise

[b] Data from reference *21*.

[c] ERA's estimate

All FLM tests have high (~95%) sensitivity, having immature results in RDS cases. All also suffer from mediocre (~65%) specificity, yielding mature results in most, but not all, cases with adequate fetal pulmonary development. The clinical outcome studies of L/S ratio,[22, 23, 24, 25, 26] FPol,[22, 27, 28, 29] TDx FLM II,[30, 31] and LBC[24, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42] have very similar results in clinical outcome studies. The quantitative results of these tests reveal the degree of pulmonary maturation and are therefore more prognostically useful to the clinician than the qualitative tests. The foam stability test[43, 44, 45, 46, 47, 48] is no longer available commercially and is used as a "laboratory developed test" by few laboratories. The turn-around time for L/S ratio is much greater than the other tests. Many laboratories have switched from L/S ratio testing to one of the rapid tests. The AmnioStat-FLM[49, 50, 51, 52, 53] is a qualitative test offered by over 400 laboratories, but in late 2003, the manufacturer was unable to supply reagents, making this test unavailable for at least 4 months.

Although there are no controlled trials evaluating cost-effectiveness of using an FLM test, there many studies, cited above, on their effectiveness of predicting fetal pulmonary status. Even though use is decreasing, there remain many FLM test requests.

Recommendation: Fetal lung maturity (FLM) testing should be available in hospitals that deliver infants. The FLM test should be available routinely once per day and in emergent

settings within an hour of specimen submission. The choice of rapid test depends on patient population:

Low risk population: qualitative PG (AmnioStat-FLM), TDx FLM II, LBC, or Foam Stability

High risk population: TDx FLM II, F Pol

Recommendation: If a rapid FLM test is available, referral of L/S ratio requests to another laboratory is acceptable practice.

Predictive Value

Because of the high sensitivity and low prevalence of RDS, the predictive value of a mature result is very good, about 98%. Conversely, the poor specificity and low prevalence produces a poor predictive value of an immature result. For example, analysis of 488 cases at the University of Utah from 1988 to 1993 showed that 43 of 135 infants with an immature L/S developed RDS. Thus, the predictive value of an immature L/S in this setting is about 32% (note that while sensitivity and specificity can be applied to different settings, predictive value can not – it depends of the prevalence of RDS). During this same time period, 7 of 353 infants with a mature L/S developed RDS. Thus the predictive value of a mature L/S is 98% in this setting.

The manufacturer of TDx FLM II (Abbott Laboratories) recommends three interpretation categories: immature (≤39 mg/g), intermediate (40-54 mg/g), and mature (≥55 mg/g). Clinical outcome studies indicate that the upper mature limit could be safely lowered.[30, 31] Using a limit of Therefore, contrary to the manufacturer's recommendation, an upper decision limit of ≥45 mg/g should improve specificity to about 85% while maintaining sensitivity at >95%.

Recommendation: use of 45 mg/g as the maturity decision threshold for TDx FLM II reduces the number of false immature results without adversely increasing the number of false mature results.

LBC tests are rapid, but the results differ by instrument.[32] LBC maturity thresholds vary dramatically from 19,000 to 50,000/μL and are caused by use of different centrifugation protocols[54] and different analyzers.[55]

Recommendation: laboratories using LBC for FLM should determine there reference values by (A) performing a clinical outcome study (B) comparing their method to a method used in an outcome study using paired amniotic fluid specimens and then adjusting the threshold or transforming the results to agree with the primary method.

Recommendation: laboratories using LBC for FLM should not use centrifugation in order to improve precision.

Blood Contamination

Blood contains a high concentration of phospholipids as compared to amniotic fluid. Therefore, the FLM results of bloody amniotic fluid specimens are altered. The exception is PG.[56,57] Even though blood contamination alters the FLM results, it does not produce false mature results.[58]

Recommendation: bloody amniotic fluid specimens should be tested for FLM. Mature and very immature results are trustworthy, whereas borderline immature results could be falsely low or high.

Meconium Contamination

The presence of heavy meconium contamination (greater than 15 g/dL) interferes with most FLM results.[59] Moderate meconium contamination (about 5 g/dL) can produce erroneous L/S ratio values from immature to mature[60, 61] and interferes with fluorescence polarization methods (TDx FLM II and FPol),[62] but does not cause false mature

AmnioStat-FLM PG results.[56, 57] LBC results increase by less than 5000/μL with light contamination.[33]

Recommendation: amniotic fluid specimens contaminated with moderate meconium (greater than 5 g/dL) should not be tested for FLM except by using PG.

Diabetes

Tight glycemic control and new treatment algorithms have significantly reduced the incidence of RDS in the diabetic pregnancy.[63, 64] While some reports indicate more RDS cases despite mature L/S ratio results,[65] others indicate no additional risk.[66, 67] For poorly controlled diabetes, the gestation at which the L/S ratio begins to rise has been reported to be both delayed[68] and not delayed[18] as compared to non-diabetic pregnancies. Agreement exists in recent studies of well-controlled diabetics, the time of the L/S ratio surge is not affected by diabetes.[18, 69]

Several TDx FLM II studies have shown that these results are reliable when used in diabetic pregnancies.[70, 71, 72]

Regardless of degree of diabetic control, the detection of PG is delayed about 1.5 weeks.[18, 73, 74] Even though many clinicians rely exclusively on PG for management of diabetic patients, there are no modern studies to support this practice.

There are insufficient outcome studies to evaluate the effect of diabetes on LBC and foam stability.

Recommendation: in diabetic patients, separate reference values are not required for TDx FLM II, FPol, L/S ratio, and PG. There are insufficient studies to evaluate the effect of diabetes on LBC and foam stability test reliability.

Twin pregnancy

RDS is a frequent complication in twin pregnancy and can be discordant, especially prior to 31 weeks.[75]

Recommendation: If testing for FLM prior to 32 weeks' gestation, sampling both sacs should be sampled.

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