

AUTHOR

Maria Lopes, MD, MS,
is an obstetrician/gynecologist
and former chief medical officer
at GHI/EmblemHealth.

Managing Costs in High-Risk Obstetrics

*The Value of Technology That Improves
Diagnostic Accuracy*

Maria Lopes, MD, MS

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INTRODUCTION

In the United States, about 12.8% of babies (more than half a million a year) are born prematurely.^{1,2} The rate of premature birth has increased by 36% since the early 1980s,¹ and it is now responsible for an estimated \$26 billion in costs to the American healthcare system annually.² Unfortunately, little progress has been made to decrease prevalence in such a serious condition.

From a managed care perspective, a premature birth constitutes a potential high-cost episode of care and high-risk pregnancies constitute a major category of high cost. In 2001, 8% of the total 4.6 million infant stays included a diagnosis of preterm birth/low birth weight, yet these accounted for 47% of all infant costs.³ Within that same time frame, a separate analysis found that approximately 4% of the Medicaid population was responsible for 48% of overall program spending.⁴ More recently, a 2012 study by OptumInsight determined that the cost for a high-risk pregnancy can approach \$57,000, compared with about \$8000 for normal birth outcome.⁵ These high-cost members translate into significant budget costs in a highly concentrated, small percentage of members.

In this paper we will identify ways in which new technology can improve the diagnostic accuracy of pregnancy-related disorders and assist in managing the costs of high-risk obstetrics.

HIGH RISK PREGNANCY AND PRETERM BIRTH

A pregnancy is considered high risk for a variety of reasons, generally categorized into those of maternal or fetal origin. Prevalent maternal factors include age (younger than 15 years, older than 35 years), multiple gestation, weight (pre-pregnancy weight under 100 lb or obesity), medical comorbidities, and a history of complications during previous pregnancies. Prevalent fetal factors include exposure to infection (eg, herpes simplex, viral hepatitis, mumps, and rubella), exposure to addictive substances (eg, cigarettes, alcohol, and illicit or abused drugs), and exposure to a variety of medications.

Preterm birth is defined as delivery before 37 weeks of gestation. It is the leading cause of neonatal death and infant mortality, often as a result of respiratory distress syndrome due to immature lung development.⁶ Babies who survive are also at high risk of neurological disability⁷ and can experience further breathing, feeding, digestive, visual, and hearing problems. Observational studies have found that a prior history of preterm birth significantly increases the risk of another in a subsequent pregnancy.⁸

**Table 1. Accuracies of Various ROM Methods in Non-Obvious Cases²¹⁻²⁸**

Biomarker Test	Sensitivity (%)	Specificity (%)
PAMG-1 immunoassay ^{21,22}	94-100	99-100
IGFBP-1 immunoassay ²³	73.9	77.8
Traditional Test	Sensitivity (%)	Specificity (%)
Ferning ^{24,25}	51-63	71-76
Nitrazine (pH) ²⁶	88	68
Pooling, AFI, ferning ²⁵	85	79
Pooling, AFI, nitrazine ²²	72	98
Traditional Test	NPV (%)	Reference
Pooling, nitrazine, ferning ²⁷	46.5	Delivery <48 h
Pooling, nitrazine, ferning ²⁸	54.5	ROM

AFI, amniotic fluid index; IGFBP-1, insulin-like growth factor-binding protein-1; NPV, negative predicted value; PAMG-1, placental alpha microglobulin-1; ROM, rupture of membranes.

IDENTIFYING AREAS FOR IMPROVED MANAGEMENT OF PRETERM BIRTH

Births that follow spontaneous preterm labor (PTL) and preterm premature rupture of membranes (pPROM) are together designated as spontaneous preterm births. Spontaneous preterm births account for approximately 70% of all premature births, whereas the remaining 30% are indicated as a result of maternal or fetal infection.⁹ Of those births classified as spontaneous preterm births, 64% are the result of PTL and 36% are the result of pPROM.

PTL is defined as the onset of active contractions at a preterm (<37 weeks) gestation. Common symptoms suggestive of PTL include: uterine activity, abdominal discomfort, change in vaginal discharge, bleeding and/or cramping. Traditional evaluation includes uterine activity monitoring and evaluation of the cervix.¹⁰ The exact mechanisms of preterm labor are largely unknown, but are believed to include decidual hemorrhage (eg, placental abruption, mechanical fac-

tors such as uterine overdistension from multiple gestation, or polyhydramnios), cervical incompetence (eg, trauma, cone biopsy), uterine distortion, cervical inflammation, drug abuse, smoking, and alcohol consumption, among others.¹¹

The definition of pPROM is spontaneous rupture of the membranes at less than 37 weeks of gestation at least 1 hour before the onset of contractions. Common symptoms include complaints of leakage in the absence of active labor. Traditional diagnostic methods include nitrazine/pH, ferning, and ultrasound. Indigo carmine intra-amniotic injection may be indicated if status remains questionable after all other methods are performed.¹²

The exact mechanisms of pPROM are largely unknown, but are believed to include: bacterial production of proteases and phospholipases, host response to blood or bacteria resulting in leukocyte activation and cytokine release, uterine weakness from overdistention, strain from preterm uterine activity, direct membrane trauma (cer-

clage or amniocentesis), or a developmental weak spot.¹¹

PTL DIAGNOSTIC METHODS: IMPROVEMENTS AND THE ASSOCIATED COST IMPACTS

Improved diagnostic methods leading to improved management can directly impact the 70% of preterm births caused by both PTL and pPROM.⁹ The past decade has seen major developments in the diagnosis of both conditions, the latter of which is now increasingly considered by managed care.

The ability for a clinician to diagnose true PTL has taken significant strides in the past 2 decades with the advent of the fetal fibronectin (fFN) biomarker test. The presence of fFN in the vagina after the 20th week is abnormal and may indicate disruption of the attachment of the fetal membranes between the uterine wall and the decidua.¹³ Prior to the availability of this assay, discerning true preterm labor from false preterm labor depended on multiple methods that were neither sensitive nor specific

**Table 2.** Costs of Making the Diagnosis of PROM in Non-Obvious Cases^{12,22,28,31-37}

Procedure	Percentage of Patients With Non-Obvious ROM That Procedure Is Used On	CPT/HCPCS	2013 Medicare Payment (per patient) ^{32,36}
Ferning test	100% ¹²	Q0114 ^{31,33}	\$9.83
Vaginal pH/nitrazine test	100% ^{12,22}	CPT 83986QW ^{31,32}	\$4.92
Ultrasound	100% ^{12,22}	CPT 76805 ³⁴⁻³⁶	\$138.34
Indigo carmine amnioinfusion	4.30% ^{22,28}	CPT 59070 ^{36,37}	\$13.59
Total cost per non-obvious ROM diagnosis	—	—	\$166.68

CPT indicates Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; PROM, premature rupture of membranes; ROM, rupture of membranes.

enough to accurately predict a time to delivery for the patient presenting with complaints of early contractions. These methods consisted of home uterine monitoring and cervical length measurements. While they had good predictive values for obvious cases (ie, uterine contractions or cervical changes), they did not serve a useful function in predicting time to delivery in the absence of pronounced symptoms.

With approval of the fFN test by the US Food and Drug Administration (FDA) (Adeza Biomedical, Sunnyvale, California) in 1997,¹⁴ this situation changed due to the high negative predictive value (99.3%) of the test for delivery within 14 days.¹⁰ Historically, the suspected PTL patient typically translated into close surveillance and home uterine activity monitoring, potential admissions, and hospitalization. With the use of the fFN test, however, evaluation of the patient was changed to a screening process that resulted in the clinician's ability to reduce uncertainty and confidently rule out PTL with a negative result.

Cost-saving implications of this test on the diagnosis of PTL can be seen in both the avoidance of unnecessary hospital admissions and unnecessary patient transfers from a medical center that does not have a level III nursery. Joffe et al reported a savings in hos-

pital admissions costs of \$486,000 annually as a result of the fFN test¹⁵ and Giles et al reported a 90% reduction of transfer costs with the use of the fFN test.¹⁶

PPROM DIAGNOSTIC METHODS: IMPROVEMENTS AND THE ASSOCIATED COST IMPACTS

Over the past century, countless approaches have been proposed for the diagnosis of premature rupture of membranes (ie, PROM).^{17,18} As was the case for PTL, the diagnosis of PROM when symptoms are pronounced (ie, gross rupture of membranes with obvious fluid leakage) is easy to make. However, in 47% of patients presenting with suspicion of rupture of membranes (ROM),¹⁹ obvious leakage from the cervix cannot be visualized and the diagnosis becomes difficult to confirm or rule out.^{19,20} As demonstrated in **Table 1**, standard diagnostic methods, including nitrazine, ferning, pooling, and ultrasound, alone or in combination with one another, have proved inaccurate in such cases.²¹⁻²⁸ In the absence of an accurate test to diagnose or rule out ROM, the patient is at a greater risk for not receiving the necessary interventions, including appropriate use of steroids. Failure to implement salutary measures can have both significant

medical and financial implications for the payer, the mother and baby, and the hospital and obstetrician. Conversely, a false positive diagnosis can lead to unnecessary hospitalizations and induction of labor.

As Table 1 shows, with the advent of the biomarker test based on the detection of placental alpha microglobulin-1 (PAMG-1) (marketed as the AmniSure ROM Test, manufactured by AmniSure International LLC, Boston, Massachusetts),²⁹ the clinician now has the ability to diagnose ROM with a rapid, noninvasive, highly sensitive, and specific test in the estimated 47% of ROM cases that are not obvious.¹⁹ PAMG-1 is a decidual protein with very high concentrations in amniotic fluid with extremely low concentrations in background cervicovaginal secretions.²⁹

Insulin-like growth factor-binding protein-1 (IGFBP-1) is another assay for ROM detection. The ROM Plus test (manufactured by Clinical Innovations LLC, Salt Lake City, Utah) is commercially available in the United States. This product carries the following warning: "The test may report positive results in patients with intact membranes and therefore decisions to induce labor should not be based solely on the ROM Plus test results."³⁰ In a recent meta-analysis

**Table 3. Potential Costs of False Negative PROM Diagnosis**^{22,25,27,28,38-40}

False Negative Rate of ROM Diagnosis of Traditional Methods ^{22,25,27,28}	Treatment	Condition	Incidence Without Treatment	Incidence With Treatment	Incidence Reduction of Condition With Treatment	DRG Cost of Condition ⁴⁰	
11%-28%	Antibiotics ³⁸	Maternal chorioamnionitis	25%	16%	34%	\$5892	
		Corticosteroids ³⁹	Neonatal infection	17%	10%	38%	\$6466
			Fetal and neonatal death	19%	14%	23%	\$1793
			Respiratory distress syndrome	26%	17%	34%	\$6198
			Intra-ventricular hemorrhage	11%	6%	44%	\$3479
			Necrotizing enterocolitis	6%	3%	54%	\$3479
			Systematic infection within 48 h	9%	5%	44%	\$6198
			Cerebral palsy	7%	4%	40%	\$3479

DRG indicates diagnosis-related group; ROM, rupture of membranes.

conducted on prospective observational or cohort studies investigating ROM tests based on the detection of IGFBP-1 and PAMG-1, sensitivities, specificities, and diagnostic odds ratios were calculated. PAMG-1 outperformed IGFBP-1 in the equivocal group, which comprised patients with uncertain rupture of membranes (sensitivity, 96.0% vs 73.9%; specificity, 98.9% vs 77.8%; PAMG-1 vs IGFBP-1 tests, respectively). The authors concluded that “Compared with its performance in women with known membrane status, the accuracy of the IGFBP-1 test decreases significantly when used on patients whose membrane status is unknown. In this latter clinically relevant population, the PAMG-1 test has higher accuracy than the IGFBP-1 test.”²³

The clinical utility of those assays rests on their accuracy. Significant financial impact may result from the use of the PAMG-1 test primarily due to: (1) reductions in costs associated with false diagnoses using traditional methods; and (2) reductions in current spending on ROM diagnosis in

non-obvious cases using traditional methods.

COSTS OF INACCURATE DIAGNOSES

When used alone, or in combination, traditional methods result in high costs due to their poor accuracy, especially when used in non-obvious cases (Table 2).^{12,22,28,31-37} This leads to important economic considerations surrounding the implications of inaccurate diagnoses including: (1) costs associated with false negative diagnoses that result in the failure to treat in a timely manner; and (2) costs associated with false positive diagnoses that result in unnecessary admissions and unwarranted induction of labor.

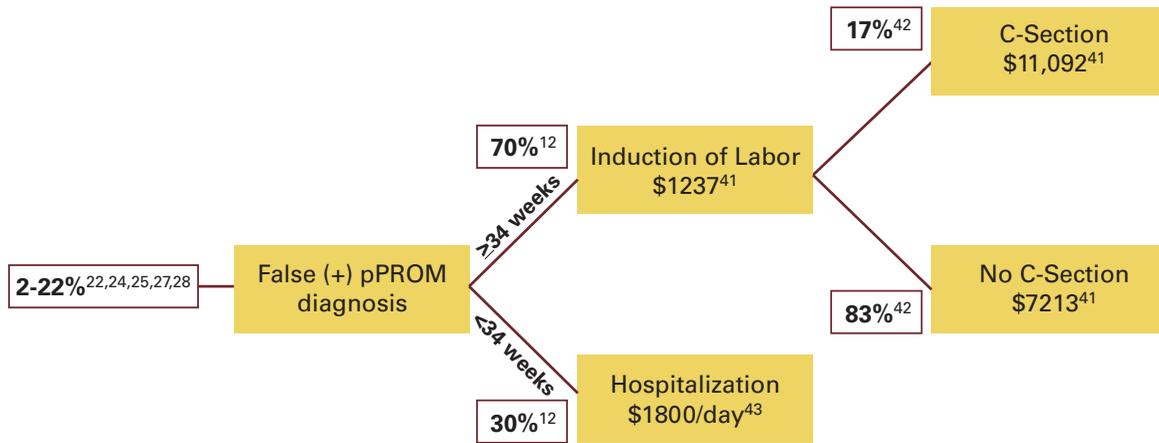
Costs of False Negative Diagnoses

Currently, there are 2 main treatments used on patients with the diagnosis of PROM: (1) prophylactic antibiotics, to fight infection and prolong latency; and (2) corticosteroids, to help mature the fetal lungs in anticipation of a preterm birth. Table 3^{22,25,27,28,38-40} summarizes multiple ran-

domized controlled trials that have demonstrated that antibiotics have a significant impact on the reduction of various conditions that may result as a consequence of PROM, including maternal chorioamnionitis and neonatal infection. Failure to administer antibiotics could result in increased risk of infection that could have otherwise been prevented or treated via the timely administration of antibiotics. By reducing the incidence of these conditions through the opportune administration of antibiotics, the costs associated with these conditions may be reduced.

As shown in Table 3 and demonstrated in multiple randomized controlled trials, corticosteroids also have a significant impact on the reduction of the various conditions that may result as a consequence of PROM, including fetal and neonatal death, respiratory distress syndrome (RDS), intraventricular hemorrhage, necrotizing enterocolitis, systematic infection within 48 hrs, and cerebral palsy.³⁹ The model depicted in Table 3 illustrates real-life DRG payments for the

Figure. Costs of False Positive Diagnosis of PROM^{12,22,24,25,27,28,41-43}



PROM indicates premature rupture of membranes; pPROM, pre-term premature rupture of membranes.

various outcomes associated with PROM that corticosteroid administration can improve. As a more specific and detailed example related to Table 3, the incidence of RDS in neonates born to a mother with PROM who did not receive corticosteroids is 34% higher than the incidence of RDS in neonates born to a mother with PROM who received a course of corticosteroids.⁴⁰ Consequently, for all cases of PROM detected by the PAMG-1 test that would have been undetected by traditional methods (see sensitivities in Table 1), a 34% reduction in the rate of RDS could be achieved.

By reducing the incidence of the various conditions associated with PROM through an accurate and timely diagnosis that allows for the appropriate intervention, the costs associated with these conditions should also be reduced.

Costs of False Positive Diagnoses

PROM occurs in approximately 10% of all pregnancies, with approximately 3% occurring during pre-term gestations and the remaining

7% occurring at term.¹¹ Therefore, close to 70% of patients diagnosed with PROM will have their delivery induced and approximately 30% will be admitted into the hospital.

Aside from the administration of treatments previously described, 2 main pathways exist for managing patients diagnosed with PROM: (1) for patients at term or late preterm (≥ 34 weeks of gestation), induction of labor is recommended; and (2) for patients at less than 34 weeks of gestation, hospitalization and observation is recommended to allow gestation to prolong.¹² Depending on the gestational age of the fetus in a patient falsely diagnosed with PROM, one of these 2 pathways would be unnecessarily followed. As the **Figure** shows, given that 2% to 22% of cases will be falsely diagnosed using various combinations of traditional methodologies,^{22,24,25,27,28} 70% of patients will be induced at a cost of \$1237 per induction,⁴¹ 17% of which will go on to have a C-section costing \$11,092.^{41,42} In the remaining 30% of falsely diagnosed patients, if the gestational age is less than or equal

to 34 weeks, the patient will likely be hospitalized at a rate of \$1800/day.⁴³ As is often the case, these patients may spend multiple days in the hospital before a diagnosis is established and discharge can occur.

COSTS OF MAKING ROM DIAGNOSIS

Table 2 outlines the costs associated with the various procedures available for diagnosing ROM. A review of the reimbursement amounts issued by the Centers for Medicare & Medicaid Services (CMS), even after adjusting for the incidence of some of the less prevalent methods (eg, indigo carmine intra-amniotic injection), determined that the costs of performing a diagnosis per patient via the typical combination of traditional methods remains greater than the costs of using the PAMG-1 test (\$166.68 vs \$88.54, which is the limit of CMS payment for the PAMG-1 test [coded as CPT 84112]).^{32,44} It should be noted that this model does not take into account the multiple iterations that each one of these methods may undergo during the full



course of evaluation, which could significantly raise the cost of making the diagnosis by traditional methods.

CONCLUSIONS

The widespread use and clinical effectiveness of the fFN and PAMG-1 assays are formally recognized in the literature. Di Renzo et al in the *Journal of Maternal-Fetal and Neonatal Medicine*⁴⁵ stated that “[The] PAMG-1 immunoassay is the most useful tool in determining women at high risk for PROM” and that “Ultrasonography to determine cervical length, fFN testing, or a combination of both [are] the most useful tools in determining women at high risk for preterm labor.”

Respected American organizations like the American Academy of Family Physicians³⁴ and guidelines like UpToDate⁴⁶ also mention the utility of the PAMG-1 assay in detecting PROM. Aside from improving quality and promoting evidence-based practice, payers benefit from the fFN and PAMG-1 tests because they directly translate clinical advantages into potential cost reductions in the management of high-risk patients.

The introduction of the fFN test into clinical practice preceded that of the PAMG-1 test by almost 10 years. Over this time, positive coverage determinations were issued by all major public and private payers on the use of the fFN test in the diagnosis of preterm labor given its clinical utility and cost-effectiveness profile.

Similarly, PAMG-1, within the first few months of having been assigned a CPT code (84112; 2011), has received positive coverage determinations by the majority of state Medicaid agencies and other private payers. Given the clinical and cost-effectiveness parallels that exist between the fFN test and the PAMG-1 test, it is expected that positive coverage for the PAMG-1 test will follow a similar path to that of the fFN test and evolve as the standard of

care to improve diagnostic accuracy in ROM. In turn, this should reduce downstream costs through appropriate triage and management.

Dr Maria Lopes is an obstetrician/gynecologist and former chief medical officer at GHI/EmblemHealth.

Address correspondence to: Maria Lopes, MD, MS, 117 Truman Dr, Cresskill, NJ 07626.

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