OBSTETRICS

Placental alpha-microglobulin-1 and combined traditional diagnostic test: a cost-benefit analysis

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OBJECTIVE: We sought to evaluate if the placental alpha-microglobulin (PAMG)-1 test vs the combined traditional diagnostic test (CTDT) of pooling, nitrazine, and ferning would be a cost-beneficial screening strategy in the setting of potential preterm premature rupture of membranes.

STUDY DESIGN: A decision analysis model was used to estimate the economic impact of PAMG-1 test vs the CTDT on preterm delivery costs from a societal perspective. Our primary outcome was the annual net cost-benefit per person tested. Baseline probabilities and costs assumptions were derived from published literature. We conducted sensitivity analyses using both deterministic and probabilistic models. Cost estimates reflect 2013 US dollars.

RESULTS: Annual net benefit from PAMG-1 was $20,014 per person tested, while CTDT had a net benefit of $15,757 per person tested. If the probability of rupture is <38%, PAMG-1 will be cost-beneficial with an annual net benefit of $16,000-37,000 per person tested, while CTDT will have an annual net benefit of $16,000-19,500 per person tested. If the probability of rupture is >38%, CTDT is more cost-beneficial. Monte Carlo simulations of 1 million trials selected PAMG-1 as the optimal strategy with a frequency of 89%, while CTDT was only selected as the optimal strategy with a frequency of 11%. Sensitivity analyses were robust.

CONCLUSION: Our cost-benefit analysis provides the economic evidence for the adoption of PAMG-1 in diagnosing preterm premature rupture of membranes in uncertain presentations and when CTDT is equivocal at 34 to <37 weeks' gestation.

Key words: AmniSure, decision analysis, premature ruptures of membrane, preterm premature ruptures of membrane

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Preterm delivery (PTD) remains the leading cause of neonatal mortality in the United States,[1,2] with 11.27% of live births reported as preterm in 2011.[3] Furthermore, PTD is associated with a massive economic and societal burden. In 2005, the annual cost of PTD in the United States was at least $26.2 billion or $51,600 per infant born preterm.[4] The etiologies of PTD include preterm premature rupture of membranes (PPROM), which is diagnosed in 33% of preterm births.[5] Therefore, an accurate diagnosis of PPROM is important because false diagnoses can cause failure to implement salutary measures[6] or lead to unnecessary obstetric interventions including iatrogenic PTD.[5,7]

The clinical diagnosis of PPROM[8] can be confirmed using a combined traditional diagnostic test (CTDT) relying on clinician's ability to document pooling, ferning, and/or positive litmus paper test. CTDT accuracy can be influenced by vaginal contamination[9] and can be uncertain or inconclusive in as low as 10% or as high as 47% of patients.[10-14] Because of these limitations, placental alpha-microglobulin (PAMG)-1 has emerged as a highly accurate biomarker in the diagnosis of rupture of membrane (ROM).[7,8,15-19] The widespread use and clinical effectiveness of the PAMG-1 assay[6] was formally recognized by the authors of the Guidelines for the Management of Spontaneous Preterm Labor.[20] However, there remains a dearth of literature that evaluates the economic aspects of adopting this technology in testing for PPROM. We conducted an analysis to compare the cost-benefit of PAMG-1 and CTDT in theoretical cohorts of patients presenting with suspicious history of PPROM ≥34 to <37 weeks' gestation.

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Materials and Methods

This study was considered exempt from institutional review board approval because it uses only a collection of publicly available and deidentified data sources. Using techniques described by Plevritis,[21] Detsky et al,[22] Naglie et al,[23] and Krahn et al,[24] we designed a cost-benefit analysis (CBA) decision tree. All computations and tree diagram were performed using a commercially available decision-analysis software (TreeAge Pro Suite, 2013; TreeAge Software Inc, Williamstown, MA) (Figure 1). The model was designed from the societal perspective. Therefore, the primary outcome was the societal net cost-benefit per person tested in the setting of potential PPROM at 34 to <37 weeks of gestation.

We focused on 34 to <37 weeks of gestation because there are numerous variables associated with the management of PPROM between 24 and 34 weeks of gestation such as: (1) types and frequency of antenatal tests; (2) course of antenatal corticosteroids; (3) choice of antibiotics and the duration of therapy; (4) frequency, duration, and choice of tocolytic agent; and finally (5) the duration of hospitalization prior to delivery. These variations will require extensive assumptions that will confound the results and conclusion. We designed a decision tree to allow us to follow the clinical scenario of a patient presenting with suspicious history of PPROM at 34 to <37 weeks of gestation. The 2 diagnostic strategies are PAMG-1 and CTDT. The PAMG-1 test result is either positive or negative for PPROM. A CTDT result can be positive, negative, or inconclusive.

There is no consensus on the timing of delivery of patients with PPROM between 34 and 37 weeks. The American Congress of Obstetricians and Gynecologists (ACOG) practice bulletin recommends induction of labor if PPROM occurs ≥34 weeks of gestation.[5] However, if expectant management is considered, it should not extend >37 0/7 weeks of gestation.[5] The Royal College of Obstetricians and Gynecologists guidelines state that delivery should be considered at 34 weeks of gestation.[25] A publication on Cochrane review on the management of PPROM <37 weeks of gestation concluded that there is insufficient evidence to guide clinical practice.[26] In view of the practice variation described above and lack of data regarding the percentage of providers who proceed with expectant management or immediate induction of labor, relevant assumptions were made.

Therefore, for the sake of the analysis, 99.9% of patients with a positive result from any of the strategies will lead to admission for immediate delivery or expectant management not to extend >37 weeks of gestation. Given the lack of data, we assumed that 70% of patients admitted for PPROM between 34 and <37 weeks of gestation will undergo expectant management, while 30% will undergo immediate labor induction. To account for the uncertainty in this assumption, we varied the range of expectant management from 30-90% during our sensitivity analysis. We estimated based on experience and data from the PPROMEXIL-2 randomized control trial: 60% of patients undergoing expectant management will proceed with spontaneous labor if they are true positive for PPROM; while 13% will be induced <37 weeks of gestation for maternal or fetal complications including but not limited to fetal distress, signs of infection, and maternal hypertensive disorders.[27] Given that patients admitted with false-positive tests for PPROM will not undergo spontaneous labor, we assumed that 99.9% of those patients undergoing expectant management will proceed with term delivery.

Neither discharge home nor admission for delivery is an appropriate option when CTDT is inconclusive at 34 to <37 weeks of gestation. ACOG guidelines recommend further evaluation when the diagnosis of ROM is inconclusive.[28] Those with inconclusive CTDT will have 3 options: (1) ultrasound assessment of amniotic fluid index (AFI) in all 4 quadrants, an AFI <8 cm will be considered positive and admitted for delivery or expectant management, while an AFI ≥8 cm will be considered negative and discharged home; (2) use PAMG-1, discharge those with negative results and admit those with positive results for delivery or expectant management; or (3) admit all patients with inconclusive CTDT for intraamniotic injection of indigo carmine, patients with positive results will proceed with delivered or expectant management, patients with negative results will be discharged home.

There is conflicting evidence to support the use of ultrasound measurement of AFI in the diagnosis of ROM.[29,30] Some publications have reported an AFI range of 8.7−10.2 cm as an optimal cutoff value in the suspicion of ROM.[31,32] A cutoff value of AFI ≤10 cm has a sensitivity of 89% and a specificity of 88.5%,[32] while a cutoff value of AFI ≤8 cm has a sensitivity of 94% and a specificity of 91%.[8,29] Therefore, it is reasonable to use an AFI cutoff value of 8 cm in our decision model. We estimate that 30-37% of ROM will have an AFI ≥8 cm. The low end of the range was author's assumption while the high end of the range was derived from MacMillan et al.[33]

The cost of the diagnostic tests used in each decision branch was included. All costs are in 2013 US dollars. Annual discounting was not required because the time horizon was within 1 year. The Centers for Medicare and Medicaid Services reimbursement cost of PAMG-1, nitrazine, ferning, and ultrasound for AFI and ultrasound-guided intraamniotic injection of indigo carmine are provided in Table 1. The weighted average costs across all 50 US states were used for our baseline analysis. The economic benefit derived from discharging patients home is the averted cost of PTD. McLaurin et al[34] reported that the total infant first-year cost for late PTD (33-36 weeks of gestation) and term delivery was $38,301 and $6156 in 2004, respectively. While there is cost associated with term delivery, health care providers and all stakeholders will all agree that interventions or practices that prevent preterm births can potentially save money for the health care system. Therefore, by sending patients home