Clinical application of amino-terminal pro-brain natriuretic peptide concentration in amniotic fluid for the prediction of preterm birth in symptomatic women

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BACKGROUND: Preterm birth accounts for 60% to 80% of neonatal mortality. Approximately one-third of preterm births are caused by the spontaneous onset of preterm labor. Nevertheless, 70% to 90% of women diagnosed with preterm labor will not deliver within 7 days. Thus, many women will be unnecessarily treated by preterm labor with risk medications. Better tools are needed to categorize women in preterm labor into high or low risk of preterm delivery.

OBJECTIVE: This study aimed to evaluate the amino-terminal pro-brain natriuretic peptide concentration in the amniotic fluid as a prognostic test to predict the risk of delivery within 48 hours or 7 days and before 34 0/7 or 37 0/7 weeks of gestation in women in preterm labor.

STUDY DESIGN: A total of 102 pregnant women presenting signs and symptoms of spontaneous preterm birth (22 0/7 to 34 0/7 weeks of gestation) were included. Amniotic fluid was obtained by amniocentesis, and amino-terminal pro-brain natriuretic peptide concentration was measured. Below normal concentration was defined as <0.5 multiples of the median of the standard curve according to gestational age. The risk of preterm delivery was estimated according to normal or lower-than-normal amino-terminal pro-brain natriuretic peptide concentrations. The predictive capacity of the test (below normal amino-terminal pro-brain natriuretic peptide concentration) was evaluated to identify spontaneous preterm birth at 48 hours or 7 days from amniocentesis and less than 34 0/7 or 37 0/7 weeks at delivery.

RESULTS: For the outcome delivery within 48 hours, lower-than-normal amino-terminal pro-brain natriuretic peptide concentration had 94.6% sensitivity, 73.8% specificity, 96.0% negative predictive value, 3.61 positive likelihood ratio, and 0.07 negative likelihood ratio. For the outcome delivery within 7 days, the test had 93.9% sensitivity, 88.7% specificity, 94.0% negative predictive value, 8.31 positive likelihood ratio, and 0.07 negative likelihood ratio. For the outcomes of spontaneous preterm birth before 34 0/7 and 37 0/7 weeks of gestation, below normal amino-terminal pro-brain natriuretic peptide concentrations had 80.0% sensitivity, 83.0% specificity, 78.0% negative predictive value, 4.70 positive likelihood ratio, and 0.24 negative likelihood ratio and 64.1% sensitivity, 91.7% specificity, 44.0% negative predictive value, 7.70 positive likelihood ratio, and 0.39 negative likelihood ratio, respectively.

CONCLUSION: Among patients in spontaneous preterm labor, the detection of lower-than-normal amino-terminal pro-brain natriuretic peptide concentrations (<0.5 multiples of the median) in amniotic fluid has an excellent predictive capacity to identify those patients at low risk of preterm delivery within 48 hours or 7 days.

Key words: amino-terminal pro-brain natriuretic peptide, amniotic fluid, preterm delivery, preterm labor

Introduction

The World Health Organization defines a preterm birth (PTB) as the birth of an infant before 37 weeks of gestation. In Chile, spontaneous PTB (sPTB) occurs in 5% to 7% of pregnancies before 37 weeks of gestation and approximately 4% of pregnancies before 34 weeks of gestation.[1] PTB accounts for 60% to 80% of neonatal mortality and 75% of severe morbidity.[2] Approximately one-third of preterm deliveries are due to the spontaneous initiation of preterm labor (PTL).[3–5]

There is no optimal intervention to prevent preterm delivery; tocolytics delay delivery but do not prevent it.[6–8] Nevertheless, there are effective

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The authors report no conflict of interest.

This study received funding from the National Fund for Scientific and Technological Development (grant number: 1141207 [J.A.C.]).

Patient consent is not required because no personal information or detail is included.

Cite this article as: Ferrer-Marquez FA, Astudillo RP, Carvajal JA. Clinical application of amino-terminal pro-brain natriuretic peptide concentration in amniotic fluid for the prediction of preterm birth in symptomatic women. Am J Obstet Gynecol Glob Rep 2024;XX:x.ex–x.ex.

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2666-5778/$36.00

http://dx.doi.org/10.1016/j.xagr.2024.100345

AJOG Global Reports at a Glance

Why was this study conducted?

This study aimed to evaluate a diagnostic test that allows categorizing between high or low risk of preterm birth among women in preterm labor (PTL).

Key findings

Normal amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels in amniotic fluid in women in spontaneous PTL correctly identified those patients at low risk of preterm delivery.

What does this add to what is known?

Knowing the NT-proBNP concentration in the amniotic fluid in women in PTL may guide clinical management and avoid unnecessary interventions in those women with a low risk of delivery within 48 hours or 7 days.

therapies to improve perinatal outcomes, such as antenatal administration of corticosteroids to induce fetal lung maturation[9–11] or magnesium sulfate administration to promote fetal neuroprotection.[12–14] In addition, it is very important to arrange a transfer to a center with appropriate neonatal care facilities.

It has been reported that 70% to 90% of women diagnosed with PTL do not deliver within 7 days, even without treatment.[15] In those cases, repeated use of corticosteroids and tocolytics can be harmful or not beneficial.[16] Therefore, researchers have studied several biomarkers to identify patients in PTL at high risk of preterm delivery to enhance targeted interventions.[17]

There are 2 commonly used tests for PTB prediction in women with spontaneous PTL (sPTL): fetal fibronectin and cervical length.[18,19] Each test accurately predicts preterm delivery risk; however, when combined, they have a better predictive value of preterm delivery.[20,21] In addition, amniotic fluid inflammatory markers have been shown to be useful in predicting preterm delivery risk in women with PTL.[22,23]

The human fetal membranes, both the amnion and chorion, synthetize brain natriuretic peptide (BNP).[24] This locally produced BNP inhibits the contraction of the human myometrium, contributing to the maintenance of myometrial quiescence during pregnancy.[25] Hence, low levels of BNP production may lead to PTB in a subset of women.[25]

The precursor of BNP (pre-proBNP) is a 134 amino acids (aa) chain. Cleavage at the 26th aa produces proBNP of 108 aa. During secretion, proBNP is divided into 2 equimolar products: BNP, the active peptide of 32 aa, and amino-terminal pro-brain natriuretic peptide (NT-proBNP), the amino-terminal portion of pro-BNP of 76 aa. The preferred method of estimating BNP concentration in a biological fluid is to measure NT-proBNP levels.[26]

We reported the normal levels of NT-proBNP in amniotic fluid during pregnancy according to gestational age at sampling.[27] In the second trimester of pregnancy, high NT-proBNP concentrations are expected, and toward the end of gestation, progressive reduction of NT-proBNP levels is anticipated.

Thus, we postulate that lower-than-normal NT-proBNP concentration in amniotic fluid may predict preterm delivery risk in PTL women. Hence, this study aimed to determine the prognostic accuracy of NT-proBNP concentration in amniotic fluid for the prediction of sPTB in patients in PTL.

Materials and Methods

Study designs

We conducted a prospective, observational, noninterventional study. Over a 6-year period, all patients admitted to our hospital (Red de Salud UC Christus) with the diagnosis of PTL were invited to participate and included in the study if they consented to participate, the inclusion criteria were met, and there were no exclusion criteria. In all amniotic fluid samples, we measured the NT-proBNP concentration, but the result of the examination was not made known to the treating team and did not affect the medical decisions adopted.

Inclusion criteria

The inclusion criteria included singleton pregnancy, gestational age determined by early ultrasound at 7 to 12 weeks of gestation, preterm labor defined as two or more regular uterine contractions in ten minutes and cervical changes defined as cervical dilation ≥ 1cm and ≥ 80% effacement, and gestational age at the diagnosis of PTL between 22 0/7 and 34 0/7 weeks of gestation. The exclusion criteria were multiple pregnancy, clinically evident chorioamnionitis, amniotic fluid compatible with intra-amniotic infection (Table 1), and fetal conditions that may alter NT-proBNP levels, such as anemia, hydrops, congenital cardiopathy, red cell isoimmunization, and fetal arrhythmia.

Procedure

Amniocentesis was performed with ultrasound guidance. After the procedure, all women received corticosteroids to induce fetal maturation and tocolysis according to local guidelines. First-line tocolytic therapy was nifedipine 20 mg orally every 20 minutes for 1 hour. Successful tocolysis was defined as 0 or 1 contraction in 10 minutes associated with the absence of cervical changes 1 hour after treatment. If tocolysis was successful, nifedipine 10 mg every 6 hours orally was maintained for 48 hours. In those cases of failure to treatment with nifedipine after 1 hour of initiation, and if intra-amniotic infection had been ruled out, a second-line treatment with intravenous fenoterol in a continuous infusion pump was started until completing 48 hours of treatment. In those cases, in which uterine contractions persisted and the active phase of labor began, tocolytic treatment was suspended, continuous fetal surveillance was maintained, and delivery care, vaginal or cesarean delivery, was prepared according to the characteristics of the patient.

TABLE 1
Criteria for the diagnosis of intra-amniotic infection

Variable	Abnormal value
Glucose concentration	<0.771 mmol/L
Lactate dehydrogenase concentration	>6.68 μKat/L
Leukocyte concentration	>50 per mm^3
Gram staining	Presence of microorganisms
Aerobic and anaerobic cultures	Positive culture
Ureaplasma and mycoplasma cultures	Positive culture

If the sample had 1 abnormal value, the case was considered compatible with intra-amniotic infection and discarded from the study.

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Sample processing

A 10-mL sample of amniotic fluid was obtained by amniocentesis. Samples were stored at room temperature until assayed and analyzed within two hours from collected to measure NT-proBNP measurement. Measurements took place at the hospital laboratory, an ISO 15189 accredited medical laboratory.

NT-proBNP was estimated by the automated Elecsys proBNP assay from Roche Diagnosis, Indianapolis, Indiana. An electrochemiluminescent immunoassay with 2 polyclonal NT-proBNP −specific antibodies was performed in a sandwich test format. The assay measuring range reported by the vendor was 5 to 35,000 pg/mL; the assay variation within-run was 1.8% to 2.7% and was 2.2% to 3.2% overall.

The cutoff threshold for low NT-proBNP values was defined as <0.5 multiple of the median (MoM) according to gestational age following the standard normality curve published.[27] The ability of low NT-proBNP values (<0.5 MoM) to predict sPTB within 48 hours, 7 days, <34 0/7 weeks, and <37 0/7 weeks of testing was assessed. Positive predictive value (PPV), negative predictive value (NPV), likelihood ratios (LR), sensitivity, and specificity were calculated.

Statistical analysis was performed with median and interquartile range values for continuous variables and number and percentage values to describe demographic and obstetrical outcomes. The rates of maternal outcomes were obtained by dividing the number of maternal outcomes by the total number of included pregnancies. The rates of perinatal outcomes were obtained by dividing the number of perinatal outcomes by the total number of newborns.

Sample size calculation

We calculated the sample size according to the guidelines for calculating the sample size in diagnostic or prognostic testing-type studies.[28] A 90% sensitivity, 80% specificity and 10% risk of delivery were postulated, with significance of 5% and power of 80%. It was estimated that 100 women should be included in the study.

Ethics

Patient data were deidentified for confidentiality purposes. The local institutional ethics committee approved the research protocol. All participants were informed and signed the consent form.

Results

A total of 102 samples of amniotic fluid of patient in spontaneous preterm labor (sPTL) were analyzed. Table 2 provides the details of the clinical characteristics of the group of patients.

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TABLE 2
Clinical characteristics of included women

Variables	N=102
Age (y)	28.70±5.43
Nulliparous	23 (22.5)
Multiparous	79 (77.5)
Previous preterm delivery	8 (7.8)
BMI (kg/m^2)	24.3±3.3
Hispanic	102 (100.0)
Gestational age at amniocentesis (wk)	30.5±2.9
Gestational age at delivery (wk)	33.8±3.8
Deliveries<48 h	33 (32.3)
Deliveries<7 d	49 (48.0)
Deliveries<34 wk	52 (50.9)
Deliveries<37 wk	71 (69.6)
Term deliveries	31 (30.4)
Vaginal delivery	69 (67.6)
Cesarean delivery	33 (32.4)
Medical comorbidities: hypertension and diabetes mellitus	10 (9.8)

Data are presented as mean±standard deviation or number (percentage).

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TABLE 3
Predictive capacity of NT-ProBNP concentration in amniotic fluid of <0.5 MoM

Delivery	Sensitivity	Specificity	PPV	NPV	LR (+)	LR (−)
<48 h	94.6%	73.8%	67.3%	96.0%	3.61	0.07
<7 d	93.9%	88.7%	88.5%	94.0%	8.31	0.07
<34 wk	80.0%	83.0%	84.6%	78.0%	4.71	0.24
<37 wk	64.1%	91.7%	96.2%	44.0%	7.72	0.39

LR (−), negative likelihood ratio; *LR (+)*, positive likelihood ratio; *MoM*, multiples of the median; *NPV*, negative predictive value; *NT-ProBNP*, amino-terminal pro-brain natriuretic peptide; *PPV*, positive predictive value.

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test of NT-proBNP in amniotic fluid, defined as a concentration of <0.5 MoM, a high sensitivity (94.6% and 93.9%) and NPV (96.0% and 94.0%) for the risk of delivery within 48 hours or 7 days, respectively. In Table 3, we present all the diagnostic performance characteristics of the test.

We detected a high capacity of NT-proBNP measurement in amniotic fluid as a diagnostic test to discard PTB risk within 48 hours or 7 days in patients in sPTL. As depicted in Table 3, low values of NT-proBNP have a significant negative LR of 0.07 for the prediction of sPTB within 48 hours and 7 days. In other words, a negative test (>0.5 MoM NT-proBNP concentration in the amniotic fluid) significantly reduces the delivery risk in the following 48 hours or 7 days.

In addition, the test has a moderate ability to predict a high risk of delivery within 48 hours, 7 days, or before 34 or 37 weeks of gestation, with positive LRs of 3.61, 8.31, 4.71, and 7.72, respectively (Table 3).

Discussion

Principal findings

Normal levels of NT-proBNP in amniotic fluid in patients in PTL best define a subgroup with extremely low risk of delivery within 48 hours and 7 days. Low NT-proBNP concentration as a prognostic test has good capacity (sensitivity, specificity, PPV, and NPV) to predict the risk of delivery before 48 hours, 7 days, or premature delivery (<34 or <37 weeks of gestation), but its main characteristic is the ability to discharge the risk of birth within 48 hours or 7 days, considering its very low negative LR. A woman in PTL has a 10.0% to 30.0% risk of delivering within 48 hours or 7 days, and that risk decreases to 0.8% to 3.0% if the BNP concentration in the amniotic fluid is normal.

This study proposed that NT-proBNP measurement in amniotic fluid can be a diagnostic test to predict sPTB in patients in sPTL. It has been well defined that a prognostic test is capable of generating important and often conclusive changes between pretest and posttest probabilities if the positive LR is >10 or the negative LR is <0.1.[29] Thus, the main finding of this research is the negative LR of 0.07 for the low NT-proBNP test in amniotic fluid. The test becomes an appropriate tool to rule out the risk of premature delivery in women in sPTL.

The most frequently used tests to predict preterm delivery risk in symptomatic women are cervical length and fibronectin.[30,31] The presence of fetal fibronectin (>50 ng/mL) or a short cervix (<15 mm) has been studied in women in PTL to improve the clinical ability to predict the risk of PTB in symptomatic women and, thus, enhance clinical management. However, the American College of Obstetricians and Gynecologists warns that although the results of observational studies have been promising, the findings have not been confirmed by randomized trials.[32] In their clinical guidelines, they state that the PPV of a positive fetal fibronectin test result or a short cervix alone is low and should not be used exclusively to guide management in women in PTL.[32] This lack of clinical use underscores the need for further research.

Recent studies on the usefulness of these markers in predicting the risk of PTB in women in PTL have been encouraging. A prospective cohort study concluded that, in multiparous women, the detection of fetal fibronectin in the cervix (regardless of the cutoff value) has low sensitivity and specificity for the risk of PTB. For multiparous women, cervicometry is recommended, with cutoff values of ≥25 or ≥20 mm, to select a low-risk population for PTB in multiparous women with or without a history of previous PTB.[30] The presence of fetal fibronectin (>20 ng/mL) in nulliparous women has a sensitivity, specificity, and NPV of 69.2%, 83.0%, and 91.1%, respectively. Researchers suggest that, in nulliparous women, a negative fetal fibronectin test allows the identification of those with the lowest risk of PTB.[30]

However, the low NT-proBNP test has better predictive capacity than the other tests to rule out delivery risk within 48 hours or 7 days. For example, a short cervix (<15 mm) in women in PTL has a negative LR of just 0.4 and 0.4 for delivery within 48 hours or 7 days,[20] and that negative cervicovaginal fibronectin has a negative LR of 0.5 and 0.4 for the same outcomes.[20] Similarly, the analysis of data from the recent cross-sectional study allows for the calculation of a positive LR and negative LR of 4.07 and 0.37, respectively, for the fetal fibronectin test of >20 mg/mL.[30] It is clear that the NT-proBNP test presented here has a much better ability to identify the group of women at low risk of delivery within the next 48 hours or 7 days than fetal fibronectin or cervical length.

Clinical implications

Clinical guidelines recommend the use of corticosteroids and tocolytics in women in PTL.[32] However, 70% to 90% of these women will not deliver within the next 48 hours or 7 days, making this

treatment unnecessary and exposing the women and fetuses to potentially risky medications. The main finding of this research is that those women in PTL in whom NT-proBNP is demonstrated within the normal range for gestational age (negative NT-proBNP test of <0.5 MoM) have a minimal risk of delivery within 48 hours or 7 days. In these women, the use of corticosteroids and tocolytics could be omitted, considering the very low risk of delivery in the period for which these medications are useful.

Research implications

Here, we have demonstrated the diagnostic ability of low NT-proBNP to predict the risk of PTB in women in PTL, concluding that it has a very good ability to rule out the risk of birth within 48 hours or 7 days. However, the clinical usefulness of this test must be demonstrated in an experimental clinical investigation, that is, in a randomized study in which a group of women in PTL is managed according to the result of the measurement of NT-proBNP or in the absence of this result, to demonstrate the implementation of the test results in a better clinical outcome than its nonuse. It is considered that a randomized clinical investigation is essential for the inclusion of a new diagnostic or prognostic test in routine clinical practice, recognizing that, sometimes, such tests may not be the best study option and that, occasionally, cohort studies can provide the best approximation.[33]

In addition, NT-proBNP testing should be compared against cervical length and fetal fibronectin, alone or in combination. It is possible that the combination of these diagnostic tests is better than each one separately, as has already been demonstrated with cervical length and fetal fibronectin.[34,35] Each test points to different causes of premature birth: cervical length looks for dysfunctional cervix, elevated fetal fibronectin suggests activation of fetal membranes, and low NT-proBNP level predicts increased myometrial contractility; thus, using several tests together can be more effective than each one alone.

Strengths and limitations

The main strength of our research was being a blind, nonexperimental clinical trial, in which all subjects were subjected to the diagnostic test, in a real clinical scenario. In this way, given the accurate calculation and completeness of the sample size, the diagnostic capacity results detected are clinically reliable.

Another very important aspect is that the measurement of the NT-proBNP concentration in a biological liquid should be available in all emergency laboratories. The NT-proBNP concentration is frequently measured in the plasma of people who present to the emergency room with chest pain to rule out the risk of heart failure.[36] We report normal levels of NT-proBNP in amniotic fluid by measuring its concentration in the same way as would have been done to measure it in plasma. In this way, any obstetrics service can easily implement the test in the same way.[27]

The main limitation of our study was that the measurement of NT-proBNP required a collection of amniotic fluid obtained by amniocentesis. This invasive procedure is not routinely used in all services in managing PTB. However, clinical recommendations routinely recommend amniocentesis in women with cervical dilation or a short cervix (<15 mm), as is the case of the women included in this investigation.[32]

Another limitation of our study was that it was conducted at a single-hospital center, and the included population was Hispanic. The NT-proBNP concentration may differ in other populations. For this reason, the normal curves of NT-proBNP and its alterations to predict the risk of PTB should be validated in other populations and ethnicities.

Conclusions

The measurement of NT-proBNP seems to be useful in clinical practice as a diagnostic test in emergency departments to estimate the risk of delivery in patients with spontaneous threatened PTL. Selecting women in PTL with a low risk of delivery within the next 48 hours or 7 days will avoid unnecessary interventions, such as corticosteroids or tocolytics. ■

CRediT authorship contribution statement

Fernando A. Ferrer-Marquez: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rocío P. Astudillo:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Jorge A. Carvajal:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. ■

ACKNOWLEDGMENTS

We would like to thank the doctors and midwives who contributed by obtaining amniotic fluid samples and caring for the patients.

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