Prediction of preterm delivery using molecular markers; "placental alpha-microglobulin-1", "fetal fibronectin" and "phosphorylated insulin-like growth factor-binding protein-1" tests

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KENT SAĞLIK GRUBU

Preterm Birth (PTB) is a global healthcare problem!

Bar chart:
- **%11,9** — Türkiye
- **%12** — USA
- **%5-9** — EU
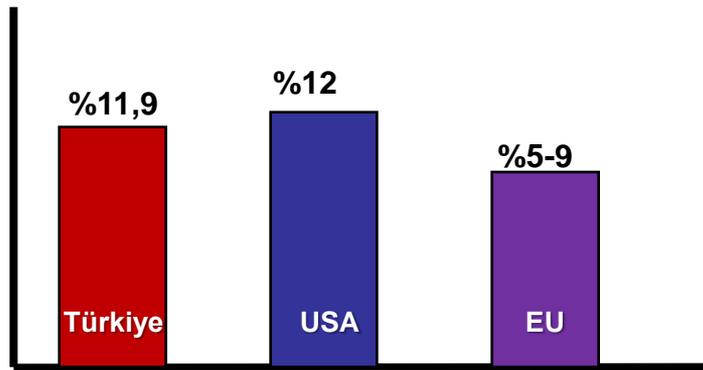
- ➢ 1st cause of death among newborns (without congenital anomalies)
- ➢ 2nd cause of death, <5 years.
- ➢ 1/2 of all neonatal neurological complications.

PTB related costs;

26 Billion $ in the USA

3 Billion £ in the UK

➢ **PTB** accounts for **3.1**% of all Disability Adjusted Life Years (**DALYs**) in the **Global Burden of Disease**, more than for *HIV* and *malaria* (including ***cerebral palsy, learning, visual, hearing and respiratory disorders, bronchopulmonary dysplasia and necrotizing enterocolitis***).

Almost 90% of women with PTL not going on to deliver within 7 days, and almost 75% will deliver at term! Ness A, Visintine J, Ricci E, Berghella V. Does knowledge of cervical length and fetal fibronectin affect management of women with threatened preterm labor? A randomized trial. Am. J. Obstet. Gynecol. 2007

Approximately 30% of PTL spontaneously resolves and 50% of patients hospitalized for preterm labor actually give birth at term! ACOG Practice bulletin no. 171: management of preterm labor 2016, Sanchez-Ramos L et al. Fetal fibronectin as a short-term predictor of preterm birth in symptomatic patients: a meta-analysis. Obstet Gynecol 2009

What do we expect from predictive tests?

Predictive tests should provide reassurance for women who are unlikely to deliver early!

To avoid unnecessary interventions like

Hospitalization

Tocolysis

Steroid administration

What do we expect from predictive tests?

Predictive tests should provide reassurance for women who are likely to deliver early!

To plan appropriate management like

Tocolysis

Corticosteroids

Magnesium sulphate

Progesterone

to organize transfer to a tertiary care center
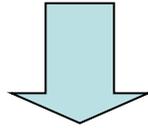
Mechanical stress   Infections
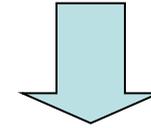
extracellular matrix degradation in the
choriodecidual junction
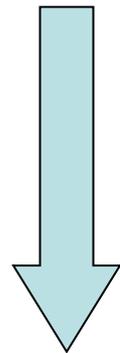
Fetal Fibronectin

phIGFBP-1

PAMG-1

cervicovaginal fluid

Tests

Qualitative

Fetal Fibronectin

1- Laboratory Qualitative Elisa immunoassay kit (Adeza, Marlborough, USA)
2. Bedside immunoGold assay kit (Adeza, Marlborough, USA)
3. QuikCheckTM dipstick tests (Hologic, Marlborough, USA)
4. Rapid fFN Cassette TLiIQ® (Hologic, Marlborough, USA)

phIGFBP-1

Actim partus (Medix Biochemica, Kauniainen, Finland)

PAMG-1

Partosure (Parsagen, Boston, USA)

Quantitative

Rapid fFN Cassette 10Q System® (Hologic, Marlborough, USA)

HOLOGIC

Rapid fFN
Specimen Collection Kit

1
2
3

STERILE POLYESTER TIPPED APPLICATOR

TLi₆

HOLOGIC® TLi™

RAPID fFN RESULT
NEGATIVE
TIME:10:03a DATE:05/12/16

PATIENT:MARY SMITH
USER:MELGAISH
CASSETTE LOT:J4047
CALIBRATION CODE:DH37
ANALYZER ID:60286

INTERNAL CONTROLS
ANALYZER: PASS
CASSETTE: PASS

TLi₆
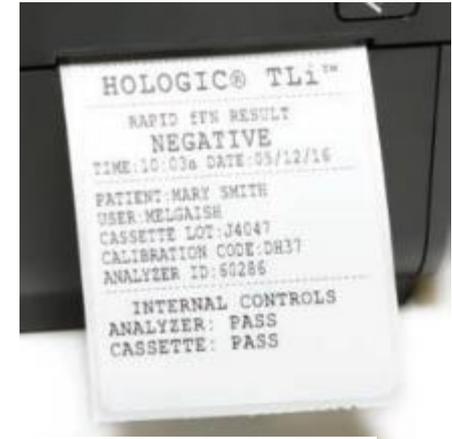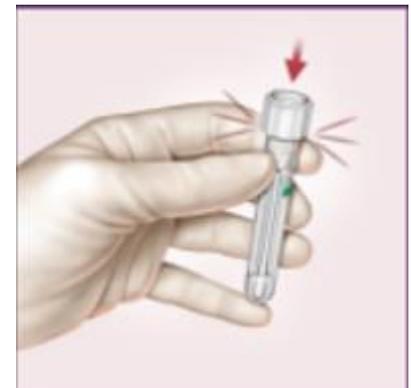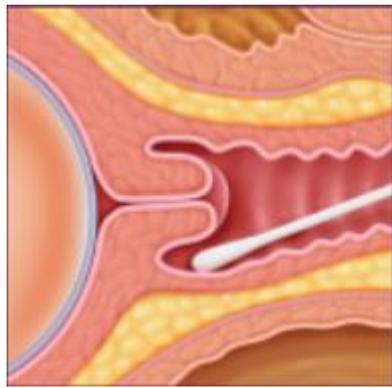
Rapid fFN®
10Q System

HOLOGIC® Rapid fFN ™

Rapid fFN 10Q POS CTL RESULT

112 ng/mL

TIME : 17: 07   DATE : 02 / 05 / 12

POS CONTROL: M1023
USER: L. BAYDOUN
CASSETTE LOT: F7031
CALIBRATION CODE: 7JHMB-S7WU3
ANALYZER ID: G0237

INTERNAL CONTROLS
ANALYZER: PASS
CASSETTE: PASS

Hologic QuikCheck *fFN*
Hologic QuikCheck *fFN*

Control Line

Test Line

Dip Area

Invalid   Invalid

positive

negative

invalid

Actim 1ngeni

PROM/ Partus test

REF 30803ETAC

DILSPE 0,5 ml

LOT 0038377   2019-06-29

25°C

2°C

x Biochemica
Finland
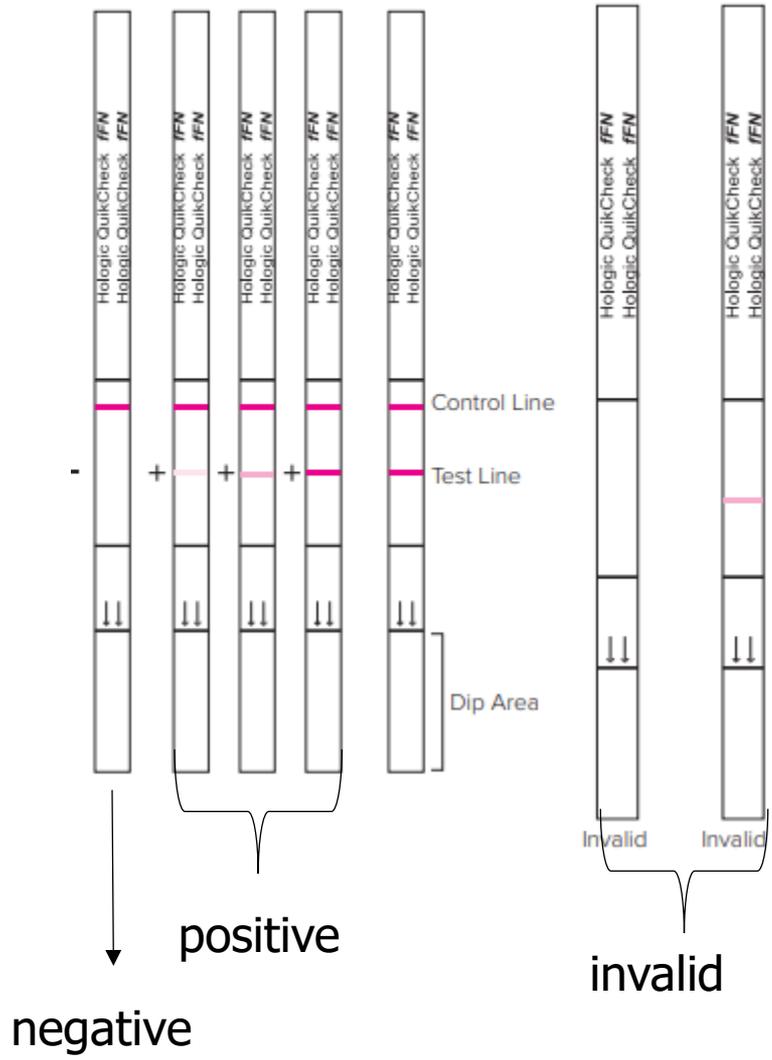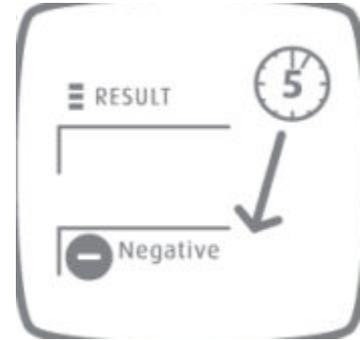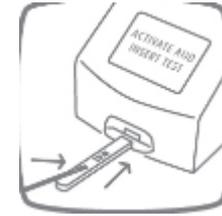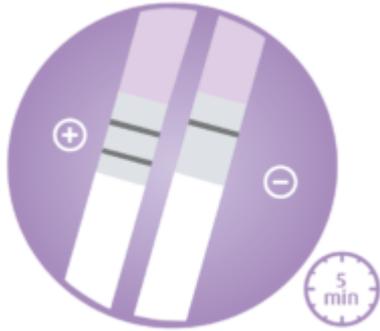
Collect sample of vaginal discharge with sterile collection swab (speculum optional).

00:00:30

Rinse specimen swab in solvent vial. Discard swab.

00:00:30
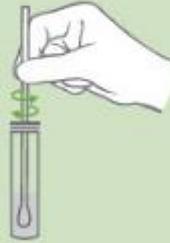
01   02

04   03
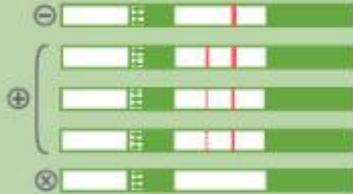
Test strip is extracted from vial and results observed and recorded.

Insert test strip into vial and remove if 2 lines are visible, or at 5 minutes sharp.

00:05:00
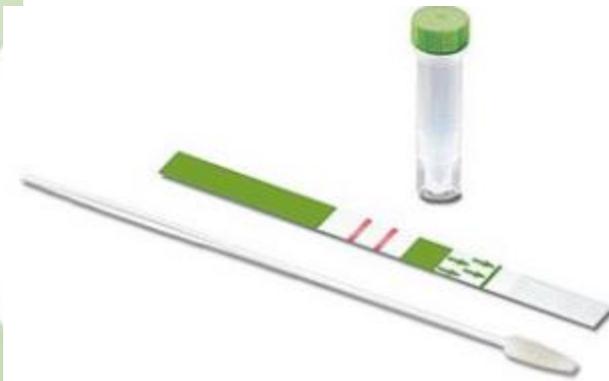
category	Rapid fFN 10Q	Actim Partus (phIGFBP-1)	PartoSure (PAMG-1)
GW	22-35^{+6}	22	20-36^{+6}
Speculum exam	needed	needed	±
Contraindications	Cx>3cm, ROM, Cerclage, Pl. Abruptio, Pl. Previa, Vaginal bleeding	ROM, vaginal bleeding, amniotic fluid	Blood on the swab, within 6 hours of disinfectants or medicines
İnaccurate tests	Sexual intercourse, digital cervical exam, TVUSG, bacteria, bilirubin, semen, a negative result is still valid if in the presence of semen		Digital exam, presence of meconium, antifungals, lubricants, moisturizers, talcum powder
Test range	0-500 ng/ml (50ng/ml)	10-8000µg/l	1-40.000 ng/ml
FDA	Approved	Approved	Approved
Costs	35£	15£	32£

Quantitative fetal fibronectin to predict spontaneous preterm birth: a review Hezelgrave NL & Shenna AH Women's Health 2015

Table 1. Prediction of spontaneous preterm birth within 2 weeks of testing according to quantitative fetal fibronectin threshold in symptomatic women (n = 300).

Predictive variable	Fetal fibronectin threshold (ng/ml)			
	10 or greater	50 or greater	200 or greater	500 or greater
Sensitivity (%)	82.4	76.5	58.8	35.3
Specificity (%)	59.3	81.1	93.9	97.5
NPV (%)	98.2	98.3	97.4	96.1
PPV (%)	10.9	19.7	37.0	46.2
Positive likelihood ratio	2.02	4.04	9.69	14.12
Negative likelihood ratio	0.30	0.29	0.44	0.66

Table 2. Prediction of spontaneous preterm birth before 34 weeks of gestation according to quantitative fetal fibronectin threshold for asymptomatic women (n = 1433).

Predictive variable	Fetal fibronectin threshold (ng/ml)			
	10 or greater	50 or greater	200 or greater	500 or greater
Sensitivity (%)	73.3	46.5	28.7	9.9
Specificity (%)	72.2	88.7	96.4	99.2
PPV (%)	16.7	23.7	37.7	47.6
NPV (%)	97.3	95.6	94.7	93.6
Positive likelihood ratio	2.64	4.10	7.97	12.0
Negative likelihood ratio	0.37	0.60	0.74	0.91

The QUiPP App: a safe alternative to a treat-all strategy for threatened preterm labor

H. A. WATSON⊙, J. CARTER, P. T. SEED, R. M. TRIBE and A. H. SHENNAN

Division of Women's Health, Kings Health Partners, Guy's and St Thomas' NHS Trust, London, UK

Quantitative Instrument for the Prediction of Preterm birth (QUiPP)

A tool to predict spontaneous preterm birth, incorporating fetal fibronectin and cervical length, in symptomatic women and high-risk asymptomatic women

QUiPP Home Symptomatic Asymptomatic User guide About Privacy Feedback

Symptomatic

1. SYMPTOMS SUGGESTIVE OF ABNORMAL OR PREMATURE UTERINE ACTIVITY? ☐ Yes • No

2. PREVIOUS CERVICAL SURGERY? • Yes ☐ No

3. PREVIOUS PRETERM BIRTH ≤36^{+6}? • Yes ☐ No

4. PREVIOUS PPROM? • Yes ☐ No

5. NUMBER OF FETUSES Select 1 ▾

6. GESTATION OF TEST Weeks 24 ▾ Days 0 ▾

7. SHORTEST CERVICAL LENGTH (MM) 23

8. fFN RESULT (NG/ML) 80

Submit Reset

Probability of spontaneous delivery

Before 30 weeks	2.9%		☐
Before 34 weeks	12.0%		☐
Before 37 weeks	24.6%		☐
Within 1 week	0.1%	25 + 0/7	☐
Within 2 weeks	0.3%	26 + 0/7	☐
Within 4 weeks	1.0%	28 + 0/7	☐

New Episode   Back

https://quipp.org/index.html

QUiPP

QUiPP

King's College London QUiPP app

Tıp

KALDIR   AÇ

Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and phIGFBP-1 tests: systematic review and meta-analysis

J. C. MELCHOR[1], A. KHALIL[2,3], D. WING[4], E. SCHLEUSSNER[5] and D. SURBEK[6]

Biomarker Test	Patients (n)	Sensitivity	Specificity	PPV	NPV	LH+	LH-
PAMG-1	2278	0.76	0.97	**0.76**	0.97	**22.51**	0.24
fFN	7431	0.58	0.84	0.34	0.93	3.63	0.50
phIGFBP-1	3192	0.93	0.76	0.35	0.99	3.80	0.09

PAMG-1 has a strong predictive accuracy for sPTB within 7days of testing in women with signs and symptoms of PTL.

PAMG-1 test is the most accurate one to be used in women with a CL between 15 and 30mm.

Management of Preterm Labor

The PPV of a positive fetal fibronectin test result is poor and *should not be used exclusively* to direct management *in the setting of acute symptoms* (Level B).

NICE National Institute for
Health and Care Excellence

Preterm labour and birth

NICE guideline
Published: 20 November 2015
nice.org.uk/guidance/ng25

- 1.7.5 Consider fetal fibronectin testing as a diagnostic test to determine likelihood of birth within 48 hours for women who are ≥30+0 weeks pregnant if TVUS CL measurement is indicated but is not available or not acceptable.

- if fetal fibronectin testing is _negative (concentration ≤50 ng/ml)_, explain to the woman that it is _unlikely that she is in preterm labour_.

- if fetal fibronectin testing is _positive (concentration ≥50 ng/ml)_, view the woman _as being in diagnosed preterm labour and offer treatment._

Taylor & Francis
Taylor & Francis Group

Check for updates

GUIDELINES

Preterm Labor and Birth Management: Recommendations from the European Association of Perinatal Medicine

G. C. Di Renzo[a], L. Cabero Roura[b], F. Facchinetti[c], H. Helmer[d], C. Hubinont[e], B. Jacobsson[f], J. S. Jørgensen[g], R. F. Lamont[h,i], A. Mikhailov[j], N. Papantoniou[k], V. Radzinsky[l], A. Shennan[m], Y. Ville[n], M. Wielgos[p] and G. H. A. Visser[o]

- Of the available biochemical tests, *fFN* has been *the best characterized*. However, the value of this test, like that of *phIGFBP-1* may be *limited only to its NPV, given its poor PPV.*

- *CL* measurement and *PAMG1/qfFN (>200ng/ml)* are *best tests* for identifying the true preterm laboring patient or excluding preterm labor.

- *In symptomatic patients where the CL is 15-30 mm*, **we recommend** the use of *a biomarker test with the highest combination of NPV and PPV*. Because of the *relatively high cost of qfFN* and according to recent literature, this test seems to be placental alpha-microglobulin-1 (**PAMG-1 Partosure**).

TEŞEKKÜRLER

Negative Predictive Value (NPV): Answers the question,
"If a woman has a negative test, how likely is she NOT to deliver prematurely?"

Positive Predictive Value (PPV): Answers the question,
"If a woman has a positive test, how likely is she to deliver prematurely?"

Sensitivity: Percent of women who have preterm delivery whom the test correctly identifies

Specificity: Percent of women who do NOT have preterm delivery whom the test correctly identifies