Biochemical Markers in the Prediction of Preterm Labor

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Preterm birth accounts for about a major proportion of perinatal morbidity and mortality which necessitates early detection of the onset of preterm labor. A number of biochemical markers in the body fluids, such as in the amniotic fluid, urine, cervical mucus, vaginal secretions, serum or plasma, saliva have been used in the detection of preterm labor.

FETAL FIBRONECTIN

Fetal fibronectin is a glycoprotein found in the extracellular substance of the decidua basalis next to the intervillosus space.1,2 Although its exact function is uncertain, it appears to be an adhesive glue at the choriodecidual junction. It is normally present in low concentrations in the vagina between 18 and 34 weeks of gestation, and its presence has been a useful marker of a pathologic disruption of the maternal–fetal interface. Levels greater than 50 ng/mL are considered positive.

Lockwood et al3 showed that fetal fibronectin had a sensitivity of 81.7% and specificity of 82.5% for detecting PTB at 37 weeks of gestation in asymptomatic patients. Iams et al4 found in a study that the patients presented with the symptoms of preterm labor (i.e., uterine contractions) and cervical dilation of <3 cm between 24 and 34 weeks of gestation, and the fetal fibronectin gives the negative predictive value of 99.5%. The presence of fetal fibronectin is found to be more accurate than the uterine contractions or cervical dilation, and it has sensitivity and specificity of 93 and 82%, respectively, with the positive predictive value of 29% for predicting delivery within 7 days and this is in accordance with the study by Peace- man et al.5 Leitich and Kaider6 found that serial sampling of fetal fibronectin in asymptomatic women at high risk for preterm delivery increased the sensitivity for delivery at less than 34 weeks of gestation to 92%, compared with 23% with a single fetal fibronectin sample.

C-REACTIVE PROTEIN

C-reactive protein (CRP) is a maternal systemic inflammatory marker and it has been evaluated as a marker of preterm birth.

C-reactive protein is a protein found in the blood, the levels of which rise in response to inflammation. It is an acute-phase reactant protein synthesized primarily by liver cells in response to the proinflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor alpha.7,8 Elevation of CRP in maternal peripheral circulation is associated with the presence of intrauterine infection.9,10 C-reactive protein is a maternal systemic inflammatory marker and it has been evaluated as a marker of preterm birth.

Hvilsom et al11 found that women with CRP concentrations ≥85th percentile (i.e., ≥7.6 mg/L) experienced a twofold increased risk of preterm delivery (odds ratio = 2.0, 95% confidence interval: 1.2–3.5) compared with women who had lower CRP concentrations.

INTERLEUKIN-6

- Interleukin-6 secretion increases due to the inflammatory reaction provoked by the bacteria ascending from the vagina reaching to pregnant uterus
- It initiates the synthesis of prostaglandins and matrix metalloproteinases (MMPs) in the decidua, chorion, amniotic fluid, leading to onset of preterm labor
- Cervical IL-6 concentrations measured at 24 weeks of gestation were elevated in women who delivered at <32 weeks of gestation.12

BETA-HUMAN CHORIONIC GONADOTROPIN

- Elevated levels of beta-human chorionic gonadotropin (beta-hCG) in cervicovaginal fluid usually in the early
second trimester is associated with the increased risk of onset of preterm labor
• A single cervicovaginal beta-hCG > 77.8 mIU/mL, between 20 and 28 weeks’ gestation, identified patients with subsequent spontaneous preterm birth with the sensitivity of 87.5% and a specificity of 97% with positive and negative predictive values of 88.5 and 98% respectively.13
• Cervicovaginal beta-hCG level > 77.8 mIU/mL was an independent predictor of spontaneous preterm birth
• Cervicovaginal beta-hCG is a sensitive and specific predictor of patients with subsequent preterm delivery.

ALPHA-FETOPROTEIN AND OTHER NEW MARKERS
• Elevated level of alpha-fetoprotein (AFP) at 24 weeks is associated with increased risk of onset of preterm labor
• Moawad et al14 reported the association of alkaline phosphatase and AFP levels with preterm birth. When alkaline phosphatase levels at 24 weeks were studied, the odds ratio for spontaneous preterm birth at <32 weeks was 6.8 (1.4–32.8) and at <35 weeks was 5.1 (1.7–15.6)
• New markers have been evaluated in various studies like vitamin D-binding protein, triggering receptor expressed on myeloid cells-1, MMP-9, MMP-3, tissue inhibitor of metalloproteinases (TIMP)-1, TIMP-2, TIMP-3, and TIMP-4, and a panel of various cytokines, chemokines, and growth factors. But they all are still in experimental phase.15,16

ESTRIOL
• Estriol is the major form of circulating estrogen during pregnancy17,18 and measurements of estriol from maternal saliva samples appear to correlate with maternal serum levels19,20
• Early estriol surge or increased level (≥2.3 ng/mL) may be clinically helpful in identifying women at elevated risk for preterm labor and birth.21,22

CONCLUSION
Fibronectin levels in cervicovaginal fluid along with cervical length are a sensitive method of detection of preterm labor.

Amniotic fluid (CRP > 110 ng/mL) had a sensitivity and specificity of 80.8% and specificity of 69.5% in prediction of preterm labor at <34 weeks.

Research shows that CRP is a nonspecific biomarker as its levels get varied with infection and other pathogenic abnormalities.

Studies shows that IL-6 in cervicovaginal fluid has the ability to detect the onset of preterm labor, whereas levels of IL-8 and IL-10 do not correlate with it.

Study by has shown that high levels of serum AFP are strongly associated with preterm birth, preeclampsia, and placental abnormalities.

High levels of beta-hCG in cervicovaginal fluid were found in women with preterm labor.

Beta-hCG test has the advantage of low cost and wide availability.

REFERENCES


