Evaluation of Predictive Value of Placental Alpha Microglobulin-1 Compared to Fetal Fibronectin in Symptomatic Preterm Delivery

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ABSTRACT:

BACKGROUND:

Placental alpha microglobulin-1 (PAMG-1) is an important biomarker for the detection of preterm labor and premature rupture of fetal membrane, also fetal fibronectin leak observed into the vagina if a preterm delivery is likely to occur and can be measured by a screening test.

OBJECTIVE:

To compare the rapid bedside test for (placental alpha microglobulin-1) with the instrumented fetal fibronectin test for prediction of imminent spontaneous preterm delivery among women with symptoms of preterm labor.

PATIENT AND METHODS:

A prospective observational study, it included 86 pregnant women between 24 – 35 weeks of gestation with singleton pregnancy, viable fetus, intact membrane, and cervical dilatation ≤ 3 cm who attend to the labor room of the hospital complaining from signs and symptoms of spontaneous preterm labor.

Patients were tested for placental alpha microglobulin-1 with the instrumented fetal fibronectin test for prediction of imminent spontaneous preterm delivery.

RESULTS:

The positive predictive values for spontaneous preterm delivery within seven days for placental alpha microglobulin-1and fetal fibronectin were 25% (4/16) and 5.6% (2/36), respectively (P= 0.001 for placental alpha microglobulin-1 superiority), while the negative predictive values were 82.9% (58/70) and 72% (36/50) for placental alpha microglobulin-1 and fetal fibronectin, respectively (P= 0.02 for PAMG-1 superiority). The sensitivity and specificity of placental alpha microglobulin-1 were (25%, and 82.9% respectively), and of fetal fibronectin were (12.5%, and 51.4% respectively).

The PPVs for spontaneous preterm delivery within 14 days for placental alpha microglobulin-1 and fetal fibronectin were 43.8% (7/16) and 11.1% (4/36) respectively (P= 0.001 for placental alpha microglobulin-1 superiority), while the NPVs were 81.4% (57/70) and 68% (34/50) for placental alpha microglobulin-1 and FFN, respectively (P= 0.001 for placental alpha microglobulin-1 superiority). The sensitivity and specificity of placental alpha microglobulin-1 were (35%, and 86.4% respectively), and of fetal fibronectin were (20%, and 51.6% respectively).

CONCLUSION:

Placental alpha microglobulin-1 performed the same as fetal fibronectin in ruling out spontaneous preterm delivery among contemporary cohort of symptomatic women but demonstrated statistical superiority in predicting it.

KEYWORDS: spontaneous preterm labor , placental alpha microglobulin-1 , fetal fibronectin

INTRODUCTION:

Preterm labour is defined as delivery of a baby before 37 completed weeks of pregnancy [(1)]. Preterm labor accounts approximately 12% of all births and is the leading cause of neonatal mortality in the United States [(2)].

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There is no evidence that the incidence of preterm birth is declining. In fact, the rate appears to be slowly increasing, in part due to an increasing incidence of multiple pregnancy [(3)].

Causes of preterm labour [(4)]

- Cervical incompetence.
- Infection
- Over-distension of uterus
- Vascular causes

- Surgical procedures and intercurrent illness
- Fetal and maternal stress
- Congenital uterine anomalies.
- Uterine fibroid.

There are several approaches to the prediction for the prediction of spontaneous preterm labour that can be divided into three general categories: risk factor assessment, cervical measurement, and biochemical markers

No single biomarker has been evolved till date, which possesses sensitivity as well as reliability for the detection of spontaneous preterm labour. Bedside tests have also been developed for detecting markers like fetal fibronectin, insulin-like growth factor binding protein-1 (IGFBP-1), interleukin-6, and placental alpha-macroglobulin-1[(5)].

Placental a microglobulin-1 is released from decidual cells and found in high concentrations in amniotic fluid. Human alpha microglobulin-1 is composed of a 183-amino-acid peptide carrying three carbohydrate chains. It belongs to a protein family, the lipocalins [(6)].It is an important biomarker for the detection of spontaneous preterm labour and premature rupture of fetal membrane (PROM). The high concentration of placental alpha microglobulin-1 in amniotic fluid means it can be used to detect if this fluid is present in the cervico-vaginal discharge of pregnant women; the presence of placental alpha microglobulin-1 in the discharge suggests that amniotic fluid is present, and therefore suggests that spontaneous preterm labour or PROM has occurred [(7)].

The concentration of placental alpha microglobulin-1 in the amniotic fluid of pregnant women is (2,000–25,000 ng/ml), while, is in cervico-vaginal discharge when the fetal membranes are intact (0.05–0.2 ng/ml). It has been found to be present in amniotic fluid in significantly high concentrations throughout all three trimesters of pregnancy [(8)].

Early research concluded a diagnostic application of placental alpha microglobulin-1 detection as a test to assess the risk of spontaneous preterm labour, a commercial test known as the Amnisure test or Partosure *test* were developed and has been shown superiority to that conventional methods for assessing the risk of preterm labour (i.e. cervical length measurement via transvaginal ultrasound) [(6)].

Fetal fibronectin is a glycoprotein present in the extracellular substance of the decidua basalis next to the intervillous space. Although its exact function is uncertain, it found to be an adhesive glue at the choriodecidual junction. It is normally present in low concentrations in the vagina between 18th and 34th weeks of gestation, and its presence has been a useful marker of a pathologic disruption of the maternal-fetal interface [(9)].

Levels greater than or equal to 50 ng/mL at or after 22 weeks have been related to an increased risk of spontaneous preterm labour. In fact, fetal fibronectin is one of the best predictors of preterm labour in all populations studied so far, and can help selecting which women are at significant risk for preterm labour [(10)]. The risk of preterm labour can be further stratified as fetal fibronectin levels of less than 10 ng/ml are associated with an even lower risk, whilst the highest risk of preterm delivery is seen with fetal fibronectin levels of greater than 200ng/ml. The accuracy in predicting spontaneous preterm labour within 7-10 days of testing among women with symptoms of threatened preterm labour, before advanced cervical dilatation, has been confirmed in large studies [(11)].

PATIENTS AND METHODS:

This is a prospective observational study that was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital during the period from 1st of Apr till 1st of Dec 2018. The study included initially 96 pregnant women between 24 – 35 weeks of gestation with singleton pregnancy, viable fetus, intact membrane, and cervical dilatation ≤ 3 cm who attended the labor room of the hospital complaining from signs and symptoms of spontaneous preterm labor, which can be defined as uterine contractions, dull backache, pelvic pressure, intermittent lower abdominal pain. Seven participants showed invalid or missing placental alpha microglobulin-1 or fetal fibronectin results, and three participants were lost to follow up, so the total number of participants included in the analysis for spontaneous preterm labor was 86.

Inclusion criteria

- Singleton pregnancy.
- Gestational age 24 – 35 weeks of gestation.
- Viable fetus.
- Intact membrane.
- Cervical dilatation ≤ 3cm.

Exclusion criteria

- Ruptured membrane.
- Cervical dilatation > 3 cm.
- Multiple gestation.

- Medically indicated preterm labor.
- Recent digital examination (In the last 24 hours).
- Recent sexual intercourse (In the last 24 hours).
- Placenta Previa.
- Moderate vaginal bleeding.
- Patients with cervical cerclage.
- Transvaginal ultrasonography or digital examination immediately before specimen collection.
- Patients who received tocolytics before specimen collection.

After taking history, general and abdominal examinations were performed, the participants investigated for the following:

- Placental alpha microglobulin-1 test
- Fetal fibronectin test

After admission to the hospital, follow up was done in the hospital while after discharging or after the single study visit, follow up was done by contact with each participant by cell phone call conversation at least 21 days after her study visit to facilitate delivery data capture. Placental alpha microglobulin-1 positive and negative predictive values were compared with fetal fibronectin positive and negative predictive values for the prediction of spontaneous preterm delivery within seven days or 14 days.

Specimen collection

- Collect sample of vaginal secretions using the sterile swab provided in kit
- With patient lying on back hold swab in middle of stick and carefully insert polyester tip of swab into vagina until fingers contact to the skin, no more than 2-3inches (5-7 cm) deep.
- Rinse swab in vial solvent for 1 minute by rotating swab, then dispose of swab
- Test the patient's sample as soon as possible after collection.
- Dip white end of strip (↓↓↓) into the correctly labeled vial of solvent.
- Allow strip to remain in vial for 10 minutes, unless 2 lines are clearly visible.
- If patient's sample is not tested within 30 minutes and sample storage is necessary, tightly close the sample vial and place in refrigerator for no more than 6 hours.
- Then speculum examination was performed for checking of status of the membrane, assessment of cervical dilation and taking sample for fetal fibronectin test.
- Cervicovaginal secretions are obtained from the posterior fornix of the vagina. The collection process is intended to be gentle. The applicator tip was lightly rotated across the posterior fornix of the vagina for approximately 10 seconds to absorb cervicovaginal secretions.
- Put the specimen swab to the into the tube. Vigorously mix the solution by rotating the swab forcefully against the side of the tube for least ten times.
- Add 3 drops (approximately 100µl) of extracted sample from the extraction tube to the sample well on the test cassette.
- Wait for the colored band(s) to appear. The result should be read at 5 minutes. Do not interpret the result after 5 minutes.

RESULTS:

The distribution of study participants by general characteristics is shown in table (1). Study participants age was ranging from 16 – 45 years with a mean of 26.63 years and a standard deviation of ± 7.21 years. More than half of study participants were aged between 20 – 29 years (53.5%) and 30.2% of them were smokers.

Regarding gestational age on sampling, it was ranging from 24 – 35 weeks with a mean of 31.72 weeks and SD of ± 2.8 weeks. The highest proportion of study participants presented with gestational age between 32 – 34 weeks (43%).

Table 1: Distribution of study participants by general characteristics.

Variable	N= 86	Percentage (%)
Age (Years)		
< 20	19	22.1
20 – 29	46	53.5
≥ 30	21	24.4
Mean ± SD	26.63 ± 7.21	
Gestational age (Weeks)		
24 - 27 $^{+6}$	22	25.6
28 – 31^{+6}	27	31.4
32 – 35	37	43.0
Mean ± SD	31.72 ± 2.8	
Smoking		
Yes	26	30.2
No	60	69.8
Residential area		
Rural	22	25.5
Urban	64	74.5
Occupational status		
Government employee	56	65.1
Housewife	30	34.9

Table (2) shows the distribution of study participants by clinical history. We noticed that 74.4% of study participants were multi gravida; 29.1% had a history of preterm labor, and 17.4% of them had a positive family history.

More than two thirds of study participants (68.6%) had a history of full term delivery and 44.2% of them had a history of previous abortion.

Table 2: Distribution of study participants by reproductive history.

Variable	N= 86	Percentage (%)
Parity		
Prim gravida	22	25.6
Multi gravida	64	74.4
Family history of preterm labor		
Yes	15	17.4
No	71	82.6
Previous history of preterm labor		
Yes	25	29.1
No	61	70.9
Previous term delivery		
Yes	59	68.6
No	27	31.4
History of previous abortion		
Yes	38	44.2
No	48	55.8
Mode of delivery	n= 36	
NVD	27	75
C/S	9	25

Pregnancy outcome of study participants is shown in figure (1). The highest prevalence of study participants was not delivered till 14 days after sampling (58.1%), while spontaneous preterm labor at 14 days or less was seen in 23.3% of them and spontaneous preterm labor at 7 days or less was occurred in 18.6%.

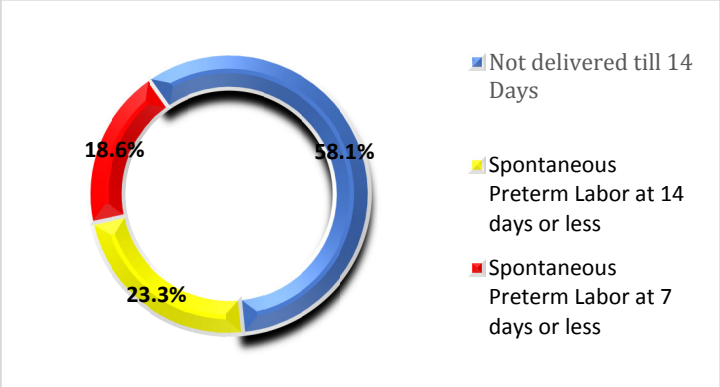

Figure 1: Pregnancy outcome of study participants.

The PPVs for spontaneous preterm delivery within 7 days for placental alpha microglobulin-1and fetal fibronectin were 25% (4/16) and 5.6% (2/36), respectively (P= 0.001 for placental alpha microglobulin-1 superiority), while the NPVs were 82.9% (58/70) and 72% (36/50) for placental alpha microglobulin-1 and fetal fibronectin , respectively (P= 0.02 for placental alpha microglobulin-1 superiority).

The PPVs for spontaneous preterm delivery within 14 days for placental alpha microglobulin-1and fetal fibronectin were 43.8% (7/16) and 11.1% (4/36) respectively (P= 0.001 for placental alpha microglobulin-1 superiority), while the NPVs were 81.4% (57/70) and 68% (34/50) for placental alpha microglobulin-1 and fetal fibronectin, respectively (P= 0.001 for placental alpha microglobulin-1 superiority) as shown in table (3).

Table 3: PAMG-1 and FFN Prediction of Spontaneous Preterm Delivery at 7 days or less and 14 days or less (Positive Predictive Value and Negative Predictive Value).

Statistics	PPV	NPV
Spontaneous preterm delivery within 7 days		
PAMG-1	25% (4/16)	82.9% (58/70)
FFN	5.6% (2/36)	72% (36/50)
P – Value	0.001	0.02
Spontaneous preterm delivery within 14 days		
PAMG-1	43.8% (7/16)	81.4% (57/70)
FFN	11.1% (4/36)	68% (34/50)
P – Value	0.001	0.001

For spontaneous preterm delivery within 7 days, the sensitivity and specificity of placental alpha microglobulin-1 were (25%, and 82.9% respectively), and of fetal fibronectin were (12.5%, and 51.4% respectively).

For spontaneous preterm delivery within 14 days, the sensitivity and specificity of placental alpha microglobulin-1 were (35%, and 86.4% respectively), and of fetal fibronectin were (20%, and 51.6% respectively) as shown in table (3.4)

Table 4: PAMG-1 and FFN Prediction of Spontaneous Preterm Delivery at 7 days or less and 14 days or less - Sensitivity and Specificity.

Statistics	Sensitivity	Specificity
Spontaneous preterm delivery within 7 days		
PAMG-1	25% (4/16)	82.9% (58/70)
FFN	12.5% (2/16)	51.4% (36/70)
Spontaneous preterm delivery within 14 days		
PAMG-1	35% (7/20)	86.4% (57/66)
FFN	20% (4/20)	51.6% (34/66)

DISCUSSION:

Preterm labour (PTL) is the single most important complication of pregnancy in the absence of congenital abnormality, as it is recognized as a global problem responsible for more than 80% of neonatal deaths and more than 50% of long term morbidity in the surviving infants [12].

The World Health Organization (WHO) factsheet found in 2012 that 15 million babies are born too early every year and almost one million children die each year due to complications of preterm labour [13].

In the present study, the mean and a standard deviation of age was 26.63 ± 7.21 years (from 16 – 45 years). (53.5%) of them were aged between 20 – 29 year and 30.2% of them were smokers. Regarding gestational age on sampling, the mean and SD was 31.72 ± 2.8 weeks (ranging from 24 – 35 weeks), gestational age between 32 – 35 weeks represented 43% of study participants.

In Wing et al [14], the mean and SD of age was 28.1 ± 5.8 years, ranging from 17–44 years, in regard to gestational age in the same study, the mean and SD was 29.7 ± 3.0 weeks, which was higher than current study.

Al-Salami et al [15] noticed a different result as found that women aged between 20-40 years represented the highest proportion (53%) among study patients.

In the current study patients, two third were delivered by normal vaginal delivery (75%); multi gravida found in 74.4%; history of preterm labour found in 29.1% and 17.4% of them had a positive family history. About two thirds of them (68.6%) had a history of full term delivery and 44.2% of them had a history of previous abortion

In comparison to other studies, Wing et al [14] found a higher result as noticed that overwhelming majority of patients had one cm dilation (96.5%), previous term delivery found in more than half of them (59.5%), 21.4% had a prior preterm labour and previous abortion found in 39.2% of study patients. In another study, Al-Salami et al [15], found nearly half of them were multiparous (52%) and majority of patients with preterm labour had previous history of such condition (78.5%).

The differences observed in the results observed among studies might be explained by different sample size included in each study, presence of the co-morbid disease, drug use during pregnancy, lack of awareness of mothers regarding the risk factors during pregnancy, and late visiting of health centers and the experts equipped for the management of preterm labour, status of fetal membrane, history of abortion and unplanned pregnancy. All these factors influenced the incidence and outcome of the pregnant women presented with preterm labour .

The PPVs for spontaneous preterm labour at seven days for placental alpha microglobulin-1and fetal fibronectin were 25% and 5.6%, respectively (P= 0.001 for placental alpha microglobulin-1 superiority), while the NPVs were 82.9% and 72% for placental alpha microglobulin-1 and fetal fibronectin, respectively (P= 0.02 for placental alpha microglobulin-1 superiority). The PPVs for spontaneous preterm labour within 14 days for placental alpha microglobulin-1 and fetal fibronectin were 43.8% and 11.1% respectively (P= 0.001 for placental alpha microglobulin-1 superiority), while the NPVs were 81.4% and 68% for placental alpha microglobulin-1and fetal fibronectin, respectively (P= 0.001 for placental alpha microglobulin-1 superiority).

Wing et al [14] found that PPV for spontaneous preterm labour within seven days or less for placental alpha microglobulin-1 was 23.1% and 4.3% for fetal fibronectin (P<0.025 for superiority). The NPVs for placental alpha microglobulin-1 were 99.5% and 99.6% for FFN (P<0.001 for non-inferiority), while the PPVs for spontaneous preterm labour within 14 days for placental alpha microglobulin-1 and fetal

fibronectin were 31% and 9.6%, respectively (P<0.025 for placental alpha microglobulin-1 superiority) and NPVs for spontaneous preterm labour within14 days or less were 98.6% and 99.3% for placental alpha microglobulin-1 and fetal fibronectin, respectively (P<0.001 for placental alpha microglobulin-1 non-inferiority).

While Melchor et al [16], in which the PPV of placental alpha microglobulin-1 and fetal fibronectin for the prediction of preterm labour within seven days was 35.3% and 7.9%, respectively, with a statistical difference in PPV for the prediction of spontaneous preterm labour within seven days of testing (P= 0.0187). The NPV values observed were 98.3 % for placental alpha microglobulin-1 and 97.9% for fetal fibronectin , there was no statistical difference in NPV for the prediction of spontaneous preterm labour within seven days of testing (P=0.7858). In concern to prediction of preterm labour within 14 days of testing in the same study, the PPV of placental alpha microglobulin-1 was 41.2% and for FFN was 7.9%, with a statistical difference in PPV within 14 days of testing (P= 0.0062). The NPV values for placental alpha microglobulin-1 and fetal fibronectin were 97.1% and 97.4%, respectively, with no statistical difference in NPV within 14 days (P= 1.0).

Within seven days or less of spontaneous preterm labour in the present study, the sensitivity and specificity of placental alpha microglobulin-1 were 25%, and 82.9%, respectively, and of fetal fibronectin were 12.5%, and 51.4% respectively. Within 14 days or less of spontaneous preterm labour, the sensitivity and specificity of placental alpha microglobulin-1 were 35%, and 86.4% respectively, and of fetal fibronectin were 20%, and 51.6% respectively.

Different results noticed in Wing et al [14] as found that sensitivity and specificity of the placental alpha microglobulin-1 test, for delivery at seven days or less, were 50% and 98.4%, respectively, while for fetal fibronectin , these results were 66.7% and 85.7%, respectively.

Additionally, Nikolova et al [17] found in their study in 2015 that sensitivities for placental alpha microglobulin-1 and fetal fibronectin in prediction of spontaneous preterm labour within seven days were 80% and 50% respectively and the specificities were 95% for placental alpha microglobulin-1 and 72% for fetal fibronectin.

The discrepancies observed among above mentioned results might have attributed to sample size of each study, since the low number of enrolled patients could not be reached for the significance prediction, the prevalence of the disease, since the diagnostic predictive values are affected by the prevalence of the disease [18], presence of other diagnostic tools, because it was found, as was expected, that higher cervical length cutoffs were associated with greater sensitivity but decreasing specificity in predicting delivery within seven days [19], type of treatment received by the patients, especially hormonal therapy (like progesterone treatment), as progesterone treatment prior to the onset of preterm labour symptoms may prolong gestation in women who subsequently experience such symptoms during their pregnancy [20] and the integrity of the fetal membranes, as the presence of placental alpha microglobulin-1 in the vagina specifically indicates a disruption in the integrity of the fetal membranes and may indirectly mean increased risk for preterm labour [21].

CONCLUSION:

We found that placental microglobulin-1 performed the same as fetal fibronectin in ruling out spontaneous preterm delivery among a contemporary cohort of symptomatic women but demonstrated statistical superiority in predicting it.

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