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Interleukins & Fetal Fibronectin Levels In Preterm Delivery

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Abstract

Although the prevention of preterm birth remains the most important challenge in obstetrics, the mechanism for the onset of preterm labor has not been fully explained. The purpose of the present study is to investigate the usefulness of cervicovaginal fetal fibronectin and certain cytokines (interleukin-1B and interleukin-8) levels during pregnancy as markers of preterm and term delivery. This study was performed on 130 pregnant women at 24 to 29 years old age. The women were classified into group I (women not in labor, n=65) and group II (women with spontaneous labor, n=65). Each group was classified into two subgroups [preterm delivery (<37 weeks gestation, n=40) and full term delivery (>37 weeks gestation, n=25)]. We obtained cervicovaginal swabs for fetal fibronectin and cervicovaginal fluids for cytokines determination.

The present study revealed that fetal fibronectin, IL- lB and IL-8 levels were significantly higher in patients in preterm labor than in patients at preterm not in labor. They were significantly higher in women at full term in labor than in women at full term not in labor.

Interleukin- lB and IL-8 obtained from women not in labor increased exponentially as gestational age increased, and the cytokines levels were significantly correlated. This study revealed that cervicovaginal measurement of fetal fibronectin, IL-lB and IL-8 in combination with clinical findings may be useful for the evaluation of patients with threatened premature delivery.

Introduction

Preterm birth is probably the most challenge problem in modern medicine *(Malak et al., 1996)*. Although preterm delivery (prior to 37 completed weeks of gestation) occurs only in 7% to 11% of births, they account for about 85% of neonatal deaths of normally formed infants *(Creasy, 1993; Copper et al., 1993)*. In addition to the increased risk of neonatal morbidity, many of survivors will be permanently handicapped or disabled *(Taylor, 1984)*. Despite significant advances in prenatal medicine, the incidence of preterm delivery has remained unchanged and stills a serious obstetric problem *(Chien et al., 1997)*.

The diagnosis of early preterm labor is difficult and is accompanied by a high false positive rate. These false diagnosis result in unnecessary and potentially hazardous treatment for thousands of women annually *(Gibbs et al., 1992 and Iams et al., 1995)*. Part of the clinical problem arises from the absence of objective criteria for the prediction or early diagnosis of preterm delivery. Unfortunately, the initial promise shown by risk scoring systems including a history of previous preterm delivery or abortion, uterine anomalies, heavy work, low socio-economic status and cervical incompetence has been limited by its poor predictive value and its populations specific analysis and predicts at best 50% of preterm deliveries *(Creasy and Merkatz 1990; Keirse, 1995)*. Cervical examination, screening for reduced breathing movements on ultrasound scanning or screening for recurrent uterine contractions provides little additional predictive power *(Lockwood,*

1994; Morrison et al., 1996). An improved method of early diagnosis would be a significant advance *(Iams et al., 1995; Burrus et al., 1995).* Recently, attention has focused on the use of biochemical markers to identify women at risk for preterm delivery *(Wennerholm et al., 1997).*

The development of biochemical markers to permit the rapid and specific identification of high-risk patients would therefore be desirable. Among the family of glycoproteins found in plasma and extracellular fluid, fetal fibronectin appears to be a good candidate *(Wiqvist 1993; Lockwood 1994; Lu et al 2001).* It has primarily been identified in amniotic fluid, trophoblastic tissue and the extracellular matrix of decidua basalis *(Langer et al., 1997). Feinberg et al. (1991),* found that fetal fibronectin immunohistochemical staining was more intense in the extracellular matrix in areas of placental attachment, more specifically, where anchoring trophoblasts are located. This glycoprotien is detectable in cervicovaginal fluid during normal pregnancy at less than 21 weeks of gestation and at full term *(Feinberg et al., 1991).* However, the presence of fetal fibronectin in the cervices or vagina after twenty weeks is abnormal *(Lockwood et al., 1991; Langer et al., 1997)* and may indicate mechanical or inflammatory mediated disruption of the choriodecidual interface and provides a possible marker for risk of preterm labor *(Leeson et al., 1996; Ness et al., 1998).*

Full term and preterm labor share a common terminal pathway that includes increased uterine contractility, cervical ripening and membrane decidual activation associated with cervical dilatation and effacement *(Gomez et al., 1994).* Cervical ripening is an active process that involves marked changes in the connective tissue of cervix *(Uldbjerg et al., 1983).* It is characterized by the degradation of collagen *(Rajabi et al., 1988),* mediated by the enzyme collagenase and elastase. The activities of these proteases are increased during parturition *(Tanaka et al., 1998).* Infiltration of neutrophils in the cervix, which may be caused by cytokines or chemotactic factors in the cervix *(El-Maradny et al., 1994, 1995),* are the main source of collagenase and elastase during parturition *(Osmers et al., 1992).* Interleukin-lB (IL-I B), a 17-kd glycoprotein synthesized mainly by monocytes and macrophages *(Dinarello 1991, 1996),* is produced in the cervix and stimulate the tissue production of collagenase and elastase *(Uchiyama et al., 1992).* Interleukin-8 (IL-8), an 8-kd glycoprotein, is a chemotacting and activating factor for neutrophils *(Baggiloilni et al., 1989).* The cervix produces IL -8 and its production is enhanced by IL-lB *(Barclay et al., 1993).* Cervical ripening is considered a physiologic inflammatory process in which IL-I B and IL-8 play an essential role *(El- Maradny et al., 1995;Franz et al., 2001).* Although elevated cytokine levels in amniotic fluid are sensitive indicators of infection-associated preterm labor *(Trautman et al 1992; Steinborn et al., 1996, 1998),* the pathophysiologic roles of cervicovaginal levels of IL-lB and IL-8 in preterm labor and parturition have not been clarified.

The relationship of the combined presence of fetal fibronectin, IL- lB and IL-8 in cervicovaginal secretions in pregnant women has not been assessed fully. The aim of this study was to investigate the reliability of the detection of these biochemical markers in the cervicovaginal secretions as predictors of preterm delivery.

Subjects And Methods

This study was conducted at Al-Zahraa hospital, Al- Azhar university and included 142 patients with singleton pregnancies between 24 and 41 weeks of gestation and intact membranes. Gestational age was calculated by date of last menstrual period and confirmed by ultrasonography done before 18 weeks of gestation.

Twelve patients included premature rupture of the membranes, oligohydramnios, congenital fetal anomalies, placenta previa, evident cervical bleeding, intrauterine growth restriction and microbial infections with the following examinations were excluded.

The participants (130 women) were classified into two groups, women not in labor (group I, n=65) and women in

spontaneous labor (group II, n=65). Samples obtained from the women not in labor were classified into two subgroups, preterm less than 37 weeks' of gestation (group A, n = 40) and full term more than 37 weeks' of gestation (group B, n =25). Samples collected from women in spontaneous labor were also classified as preterm (group C, n = 40) and full term (group D, n=25).

After consent informed was obtained, each subject was examined with a vaginal speculum to collect specimens for microbial study, fetal fibronectin, IL-1B and IL-8. Digital examination of the cervix was then performed to assess cervical dilatation and effacement. All the patients who were admitted because of symptoms suggestive of preterm labor showed uterine contraction at a rate of 4 per 20 or 8 per 60 minuets, cervical effacement of > 80% and cervical dilatation equal to or not more 2 cm. Preterm labor was defined by the tocolytic index score and diagnosed if the tocolytic index score was >1 and the patients required tocolysis.

Sampling and biochemical assays:

Cervical infection with Neisseria gonorrhoeae was evaluated by culture after plating on chocolate agar and Chlamydia trachomatis was evaluated by enzyme-linked immunoassay. Trichomonas vaginalis and Candida albicans were identified either by microscopic examination of cervical discharge diluted with saline solution or by culture. Aerobic organisms and group B streptococci were identified by standard biochemical tests after plating on 5% sheep blood agar, chocolate agar and MacConkey's agar plates *(Tanaka et al 1998., Adair et al 1998).*

Fetal fibronectin was determined quantitatively with an enzyme linked immuneosorbent assay (Fetal Fibronectin Enzyme Immunoassay; Adeza Biomedical, Snnyvale, California, USA) using monoclonal antibody FDC-6. The sample was taken with a sterile polyester swab from the commercially available collection kits. The swab was rolled gently in the posterior vaginal fornix and the cervix for 5-10 seconds, avoiding bloody areas when possible and extracted in 750 *u*L of the provided buffer solution. The sample was then stored at -80^{0}C until assay *(Morrison et al., 1993).* The absorbency of the samples and standards was then determined in duplicate by use of an automated microtiter plate reader. Absolute fetal fibronectin concentrations were obtained and recorded in micrograms per milliliter and a value of >0.05 ug/ ml was considered as positive *(Lockwood et al., 1991).*

Specimens for IL-1B and IL-8 were assayed with enzyme-linked immuonosorbent assays (ELISA) (Quantidne, R&D, Minneapolis, Minn. USA). For this assay, sterile saline solution (3 ml) was instilled in the posterior vaginal fornix with a 5-ml plastic syringe and was subsequently aspirated from the posterior fornix with the same syringe *(Anai et al ., 1997).* The amount of the fluid retrieved was 3.5 $\pm$ 0.2 ml (n = 22), the specimens were immediately centrifuged at 1800 g for 5 minutes at room temperature and stored at -80^{0}C until assay of cytokines. For this assay the interassay coefficients of variation were 43% to 72% and 7.4% to 12.4% for IL-1 B and IL-8, respectively.

All results were expressed as mean $\pm$ SE, and a P value < 0.001 was considered statistically significant, the cervical dilatation, was determined by simple regression analysis. The data were analyzed with student's *t* test for parametric data and person correlation techniques where appropriate, P<0.001was considered significant.

Results

The results of the present work could be summarized in the next two tables and five figures.

The concentrations of IL-1B was significantly higher in women in preterm labor (104.5 $\pm$ 4.76 pg/ml) than in women at preterm not in labor (24.55 $\pm$ 1.90 pg/ml) and was significantly higher in women at full term in labor than in women at full term not in labor (218.56 $\pm$ 7.52 pg/ml vs, 127.20$\pm$ 7.36 pg/ml) respectively, Table (1) .fig (1).

IL-8 concentration was also significantly higher in women in preterm labor (2273.85 ± 57.22 pg / ml) than in women at preterm not in labor (503.875 ±22.75 pg/ml) and was significantly higher in women at full term in labor than in women at full term not in labor (5087.68 ± 398.491 pg/ml vs, 2575.76± 79.79 pg/ml) Table (1) fig (2).

There was a significant correlation between the IL-1B, IL-8 levels and the degree of cervical dilatation among women at term in labor (n=40, r= 0.492, p< .002) and (n=40, r = 0.708, p< .001) respectively Table (1) & Fig (3), (4).

Cytokine IL-1B and IL-8 concentrations increased exponentially as the gestational age increased in women not in labor (n=65, r= 0.728 for IL-1B at p<0.001; and, r= 0.695 for IL-8, p<0.001, Figs 3 and 4). Concentrations of IL-1B and IL-8 were significantly correlated (n=65, r= 0.898, p<0 .001), Fig (5).

There was also a significant correlation between the cytokines and gestational age in spontaneous labor group (r= 0.825 for IL-1B, at p ≤ 0.001) fig 6 and (r=0.553 for IL-8 at p ≤ 0.001) fig 7. Regarding the correlation between IL-1B and IL-8 in this group, there was a significant correlation fig (8).

All patients who in spontaneous labor were delivered their babies after 1 to 2 days from sampling. Among fetal fibronectin positive patients who delivered preterm, the mean concentration was 0.300 ± 0.008 µg/ml compared with 0.421± 0.017 µg/ml in women who delivered at full term (table 1). Fetal fibronectin values were significantly higher in full term and preterm women in spontaneous labor than in women not in labor (both full term and preterm), (fig 9).

At the cut-off 0.05 µg/ml of fetal fibronectin, it has a specificity of 90.71% and a sensitivity of 87.6 %, positive predictive value of 90.4% and the negative predictive value of 88.0 % table (2).

Tab.(1): The descriptive statistics and the significance of IL-1B(pg/ml), IL-8 (pg/ml) and Fibronectin (µg/ml) in the four studied subgroups.

	IL-1B (pg/ml)				IL-8 (pg/ml)				Fibronectin (µ g/ml)			
	Not in Labor		Spontaneous Delivery		Not in Labor		Spontaneous Delivery		Not in Labor		Spontaneous Delivery	
	Pre term	Full term	Pre term	Full term	Pre term	Full term	Pre term	Full term	Pre term	Full term	Pre term	Full term
Mean	24.550	127.200	104.500	218.560	503.875	2575.760	2273.850	5087.680	0.055	0.057	0.300	0.420
S.E	1.905	7.369	4.760	7.527	22.750	79.799	57.229	398.491	0.001	0.005	0.008	0.017
Median	21.500	127.000	107.000	214.000	549.000	2671.000	2240.500	5764.000	0.055	0.054	0.305	0.439
S.D.	12.051	36.844	30.103	37.634	143.884	398.993	361.947	1992.454	0.004	0.027	0.051	0.085
Rang	51.000	140.000	110.000	148.000	553.000	1150.000	1528.000	6555.000	0.013	0.101	0.224	0.317
Minimum	9.000	58.000	42.000	149.000	228.000	2019.000	1450.000	226.000	0.049	0.014	0.204	0.204
Maximum	60.000	198.000	152.000	297.000	781.000	3169.000	2978.000	6781.000	0.062	0.115	0.428	0.521
Sum	982.000	3180.000	4180.000	5464.000	20155.000	64394.000	90954.000	127192.000	2.205	1.413	11.985	10.506
Count	40	25	40	25	40	25	40	25	40	25	40	25
Sig. From Not in Labor		Increase	Increase	Increase		Increase	Increase	Increase		Decrease	Increase	Increase
Pre term		P≤0.001	P≤0.001	P≤0.001		P≤0.001	P≤0.001	P≤0.001		NS	P≤0.001	P≤0.001
t value		13.487	15.594	24.987		24.969	28.740	11.484		0.399	30.333	21.466
Sig. From Not in labor			Decrease	Increase			Decrese	Increase			Increase	Increase
Full term			P≤0.001	P≤0.001			P≤0.005	P≤0.001			P≤0.001	P≤0.001
t value			2.588	8.673			3.074	6.181			25.134	20.400
Sig. From Spontaneous Dellivery				Increase				Increase				Increase
Pre term				P≤0.001				P≤0.001				P≤0.001
T-value				12.808				6.990				6.414

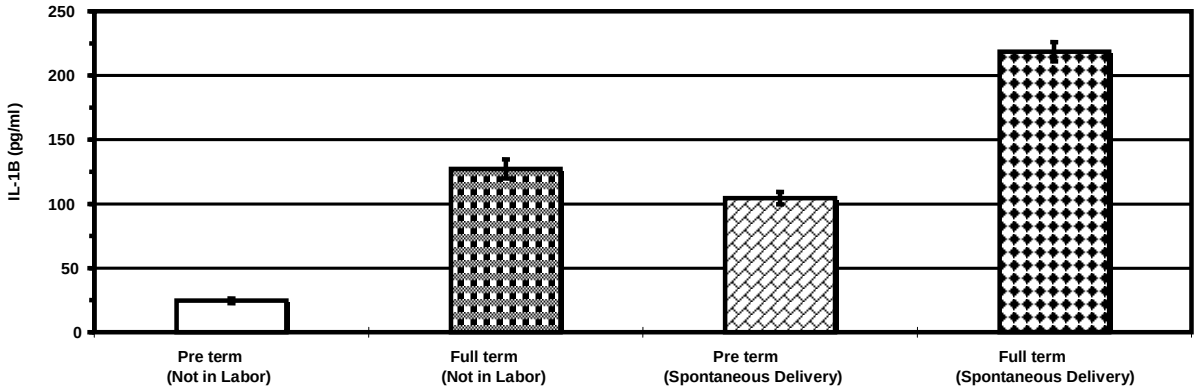

Fig. (1) : Changes in IL- 1B (pg/ml) in the four studied subgroups (mean + S.E.).

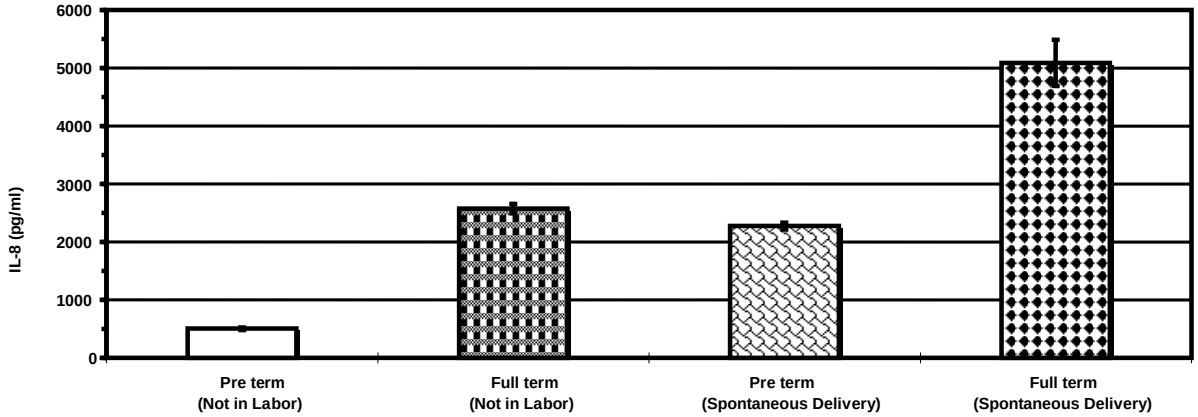

Fig. (2) : Changes in IL- 8 (pg/ml) in the four studied subgroups (mean ± S.E.).

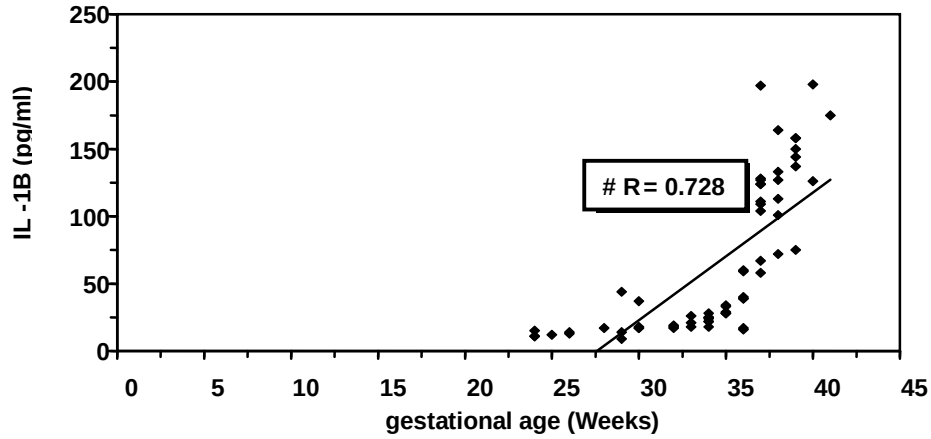

Fig. (3) : The correlation between IL1 B and gestational age in Not in labor Group .

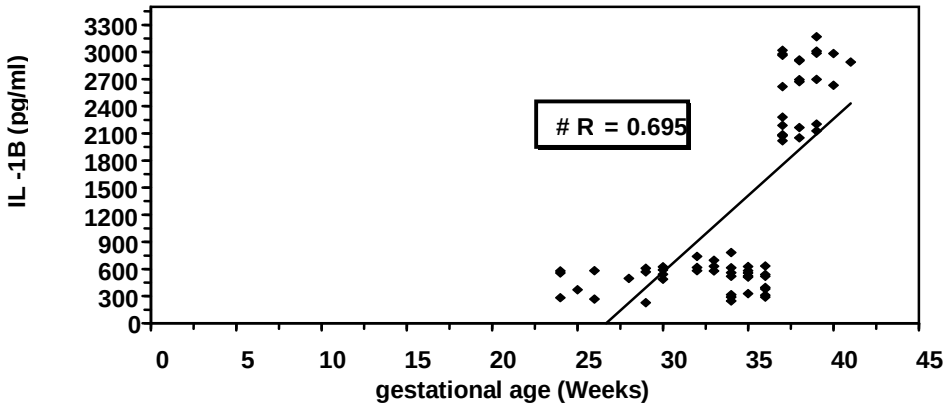

Fig. (4) : The correlation between IL- 8 and gestational age in Not in labor Group .

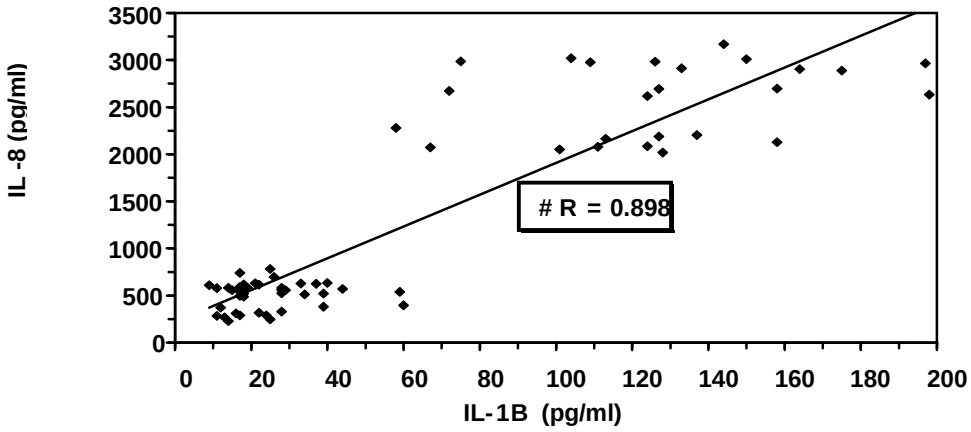

Fig. (5) : The correlation between IL- 1 B and IL- 8 in Not in Labor Group .

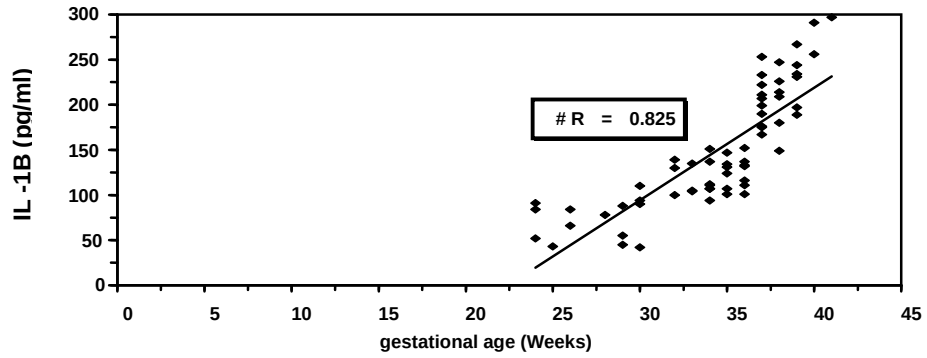

Fig. (6) : The correlation between IL- 1 B and gestational age in Spontaneous Delivery Group .

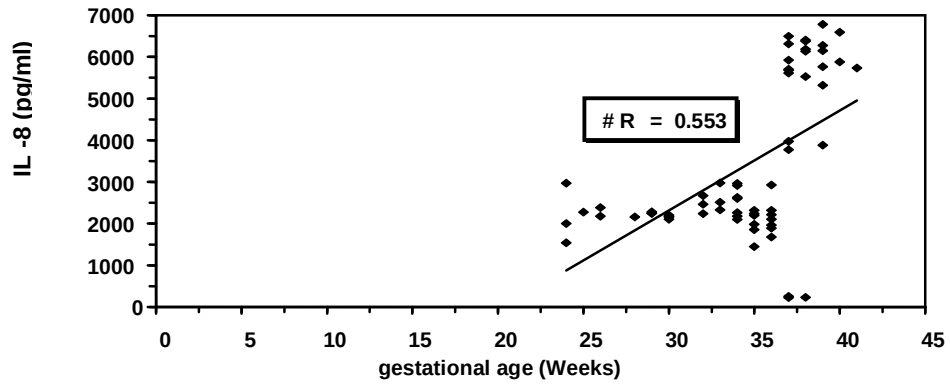

Fig. (7) : The correlation between IL- 8 and gestational age in Spontaneous Delivery Group .

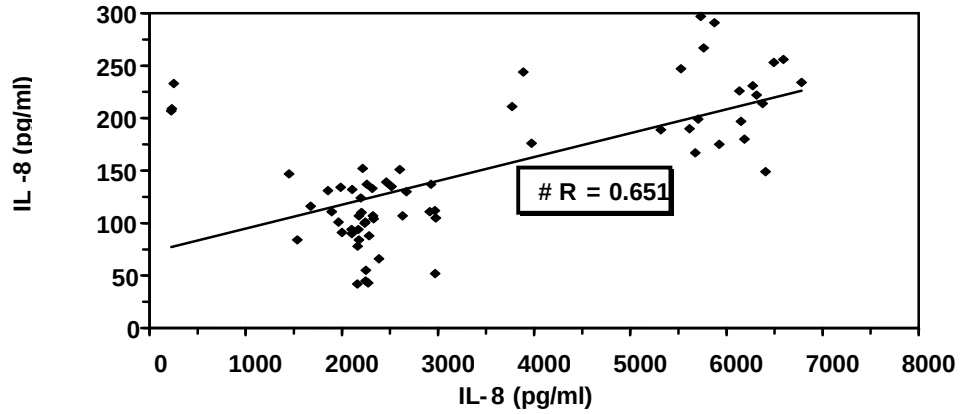

Fig. (8) : The correlation between IL- 1 B and IL- 8 in Spontaneous Delivery Group .

Table (2): The values of positive and negative cervicovaginal fetal fibronectin at preterm and full term of gestation in spontaneous labor and not in labor groups.

GROUP IN SPONTANEOUS LABOR			
	Fetal fibronectin > 0.05 μg/ml	Fetal fibronectin < 0.05 μg/ml	total
Preterm <37 weeks	35 (87.5 %)	5 (12.5 %)	40
Full term > 37 weeks	22 (88.0 %)	3 (12.0 %)	25
	57	8	65
GROUP NOT IN LABOR			
	Fetal fibronectin < 0.05 μg/ml	Fetal fibronectin > 0.05 μg/ml	total
Preterm <37 weeks	36 (90.0 %)	4 (10.0 %)	40
Full term > 37 weeks	23 (92.0 %)	2 (8.0 %)	25
	59	6	65

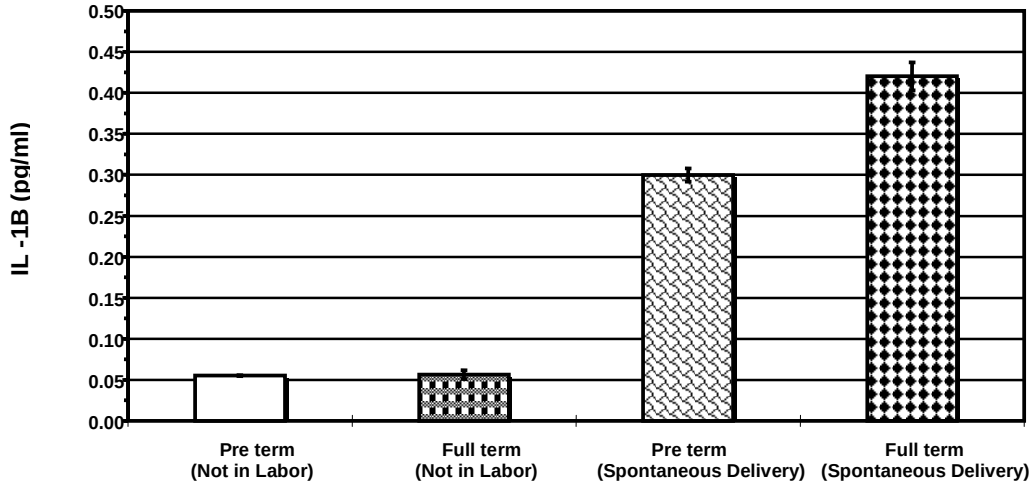

Fig. (9) : Changes in Fibronectin (μ g/ml) in the four studied subgroups (mean ± S.E.).

Discussion

This study was one of the firsts to evaluate the combined use of fetal fibronectin and cytokines (IL-1B and IL-8) as methods of identifying women at high risk of early delivery. *Mitchell et al.(1993). and Reisenberger et al. (1998),* suggested that gram negative microorganisms on contact with amnion cells, have particularly high potential for stimulating prostaglandin E_2, which is known to be a major inducer of uterine contractility. In this study, all cases with bacterial infection were excluded to avoid the pathophysiology of infection-induced preterm labor.

The uterine cervix is a rigid, closed structure consisting mainly of connective tissue that retains the uterine contents during pregnancy. Between gestational weeks 37 and 41 the uterine cervix becomes soft and dilates to accommodate the passage of the fetus. If dilatation of the cervix occurs too early, the pregnancy may be terminated prematurely. Studies have suggested that IL-lB and IL-8 play

important roles in cervical ripening *(Romero et al .,1992; Cherouny et al., 1993).* IL- lB accelerates the production of collagenase in the cervix *(Ito et al., 1988)* and stimulates the production of elastase in cervical fibroblasts *(Ito et al., 1990).* IL-8, a potent chemokine for neutrophils, induces the activation and migration of cells from vessels into the surrounding uterine cervical tissue and stimulates the release of collagenase and elastase *(Kanayama et al ., 1991;Osmers et al., 1992; Franz et al; 2001)* in the tissue, resulting in the digestion of collagen fibers during preterm and term labor. A role for IL-8 in physiologic processes during parturition was suggested by *Romero et al., (1991),* who demonstrated that spontaneous labor was associated with an increased amount of IL-8 in amniotic fluid. *El-Maradny et al. (1996)* suggested that stretching of the lower uterine segment and the amnioc-horion increase IL-8 production and collagenase activity, providing further support for the role of IL-8 in human parturition. In our study cervicovaginal fluid levels of IL-I B and IL-8 increased exponentially until term in women not in labor without any evidence of cervico-vaginal infection. Concentrations of these cytokines increased further during labor, which is consistent with the findings of *Cox et al., (1993)* for IL-lB. These observations suggest that IL-lB and IL-8 play important roles in the physiologic process of women parturition. Cervicovaginal fluid concentr-ations of IL-lB and IL-8 were positively correlated in women not in labor. IL-8 production by the uterine cervix is stimulated by IL-lB *(Osmers et al., 1995).* IL-IB and IL-8 cooperatively accelerate the production of collagenase and elastase *(Ito et al., 1988, 1990).* These observations indicate the presence of a cytokine network in the mechanism involving cervical soften-ing. In our study concentrations of IL-lB and IL-8 were higher in cervicovaginal fluids from women in preterm labor than in those from women at preterm not in labor.

Detection of fetal fibronectin in cervicovaginal secretions represents a novel approach to identifying patients at high risk for preterm birth among symptomatic *(Lockwood et al., 1991, Morrison et al., 1993; Paternoster et al., 2000)* and asymptomatic *(Lockwood et al., 1993, Nageotte et al., 1994)* populations. The mechanism of the release of fetal fibronectin in these secretions remains unknown. *Malak et al., (1994)* reported the presence of novel zone of altered structure within the rupture site of the term spontaneously ruptured fetal membranes. The release of the fetal fibronectin from the disrupted choriodecidual interface and the dissociated membrane connective tissue that characterized this zone. The altered membrane structure may be due to decidual membrane activation that may occur as a part of a common terminal pathway in both term and preterm birth to allow separation of the lower pole of fetal membranes from the decidua of the lower uterine segment *(Goldenberg et al, 1996).* Inflammatory processes that may disrupt the fetal fibronectin along the choriodecidual interf-ace and then promote further membrane degradation and uterine contractions via proteases may induce this activation and prostaglandin mediated mechanisms *(Mitchell et al., 1991).* At parturition, the destruction of the basement membrane results in, releasing of fetal fibronectin which seeps into the space between the decidua and the membranes and eventually finds its way to cervix and vagina. In this study we found that cervicovaginal fetal fibronectin levels were higher in women in preterm labor than in those from women at preterm not in labor and were significantly higher in women at term in labor than in women at term not in labor. *Faron et al. (1998)* found that the presence of fetal fibronectin in cervicovaginal secretions is associated with delivery before 34,35 or37 weeks in both high and low risk women. Finally our findings suggest that increased levels of fetal fibronectin, IL-lB and IL-8 may be associated with both labor and the progression of cervical dilatation and that measurement of cervicovaginal fluid levels of these markers could be clinically useful in predicting the onset of labor and detecting the patients with preterm delivery.

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تقدير مستويات الانترليوكين و الفيبرونيكتين كدلال لموعد الولادة

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** الهيئة القومية للرقابة والبحوث الدوائية – قسم الفارماكولوجى – (وحدة البكتريولوجى والمناعة)

بالرغم من ان منع الولادة المبكرة يعتبر من اكبر التجديات فى الولادة . فان ميكانيكية الولادة المبكر ليست واضحة .

الغرض من هذه الدراسة توضيح مدى فائدة تقدير مستوى الفيبرونيكتين للمواليد فى الرحم وبعض مستويات السيتوكين (الانترليوكين B1 والانترليوكين –8) خلال الحمل كدلالة للولادة التامة والولادة قبل الموعد .

هذه الدراسة تمت على 130 امراة حامل ذوات اعمار تتراوح من 24-29 عام السيدات التى شملهن البحث تم تقسيمهن الى مجموعات :-

المجموعة (1) نساء ليست فى حالة وضع الجنين (وعددهن 65)

المجموعة (2) نساء فى حالة وضع تلقائى للجنين (وعددهن 65)

كل مجموعة من هذه المجموعات تم تقسيمها الى مجموعتين

1. ولادة قبل الموعد (اقل من 37 أسبوع حمل)
2. فترة حمل كامله (اكثر من 37 أسبوع حمل)

تم اخذ مسحات من عنق الرحم لتحديد قيمة الفيبرونيكتين للجنين وايضا مسحات من السائل الموجود فى عنق الرحم والرحم لتحديد مستوى السيتوكين .

النتائج

وقد كان مستوى الفيبرونيكتين IL-8-IL-B1 فى حالة زيادة فى الادلة الاحصائية فى حالة السيدات اللاتى لسن فى حالة وضع وتعانين من ولادة مبكرة عن السيدات الاخريات وكانوا اكثر ارتفاعاً فى السيدات التى يلدن بعد 37 اسبوع عن السيدات الحوامل فى 37 اسبوع ولسن فى حالة ولادة .

هذه الدراسة اوضحت ان تقيم مستوى الانترليوكين فى العنق الرحمى IL-1B, IL8 بالاضافة للفحص الاكلينيكى يمكن ان يكون ذو فائدة لمعرفة الولادة المهددة بالولادة قبل الموعد.