

HUMAN FIBRONECTIN

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Abstract: Mechanisms of premature birth do not differ fundamentally from the physiological mechanisms of birth, being involved in time-immuno-endocrine system of the load and the axis of the hypothalamo-pituitary-maternal and fetal suprarenal, limiting the cost of biological aggression. Risk factors of premature birth are both maternal and fetal and can be considered aggressors triggering mechanisms of fetal and maternal defence and may lead to immature delivery. In interpreting the causes of premature birth, human fibronectin biomarker may be valuable. If you account for the many cellular changes that occur during pregnancy, fibronectin is involved in processes of cellular adhesion, migration and cellular differentiation, interaction matrix-cytoskeletal, phagocytosis, in the processes of hemostasis, wound healing, and healing in burn softening and immunological processes and malignant transformation. Mother's pre-pregnancy pathology and pathology due to pregnancy lead to the change of values of fibronectin. Human fibronectin may be a biochemical parameter of prediction, diagnosis, evolution and treatment monitoring even of premature birth by dosing the proper interpretation of the dynamic and determined values, knowing its molecular behaviour.

Cuvinte cheie: fibronectina umană, naşterea prematură, glicoproteină

Rezumat: Mecanismul naşterii premature nu diferă fundamental de mecanismele fiziologice ale naşterii normale, fiind implicat sistemul imuno-endocrin şi sistemul hipotalamo-hipofizar matern şi fetal, cu limitarea costurilor agresivităţii biologice. Factorii de risc materni şi fetalii pot fi consideraţi triggeri ai naşterii premature. În interpretarea cauzelor naşterii premature fibronectina umană este un marker biochimic valoros. Dacă se ţine cont de modificările celulare care apar în timpul sarcinii, fibronectina umană este implicată în procesele de aderenţă celulară, migrare şi diferenţiere celulară, interacţiune matrice-citoscheleton, fagocitoză, în procesele de hemostază, cicatrizarea plăgilor şi în procesele imunologice şi de transformare malignă. Bolile intervenite pe parcursul sarcinii sau cele preexistente sarcinii modifică valoarea fibronectinei umane, fie ea serică, plasmatică, din secreţia vaginală sau din lichidul amniotic. Fibronectina umană este un parametru de predicţie, de diagnostic, de evoluţie, prognostic şi chiar de monitorizare a tratamentului naşterii premature prin dozări în dinamică a acesteia şi o bună interpretare a valorilor, cunoscând comportamentul molecular al acesteia.

Fibronectin (FN) is one of the most versatile proteins known and studied, both structurally and functionally. Fibronectin is present in the human body under two forms:

- a soluble form in plasma, and other biological fluid (amniotic fluid, cerebrospinal fluid, urine, semen, cervico-vaginal discharge) synthesized in the liver by hepatocytes. Plasma concentration of FN has varied 300 -400 µg/ml, depending on the biochemical method of determination, age and gender, men's FN value was higher than women's. A significant increase in the concentration of FN depending on age is found in both genders, from decade 3 to 4 of life. (1) Plasma level of fibronectin is 15-30% higher than the seric one, knowing that fibronectin along with fibrinogen (fibrinogen fibrin stabilizing factor XIII) play a part in the formation and strengthening of the network of fibrin. (3)
- insoluble form, known as the major component of the fibrillar matrix, secreted by different cells; this form of the FN was discovered for the first time in culture medium of fibroblasts. Other cells containing FN are: hepatocytes,

epithelial cells, endothelial cells, macrophages, gliocytes, melanocytes, adherent cells in bone, chondrocyte, sinoviale, blood cells, Schwann cells, platelets, and last but not least, amniotic cells.

FIBRONECTIN STRUCTURE:

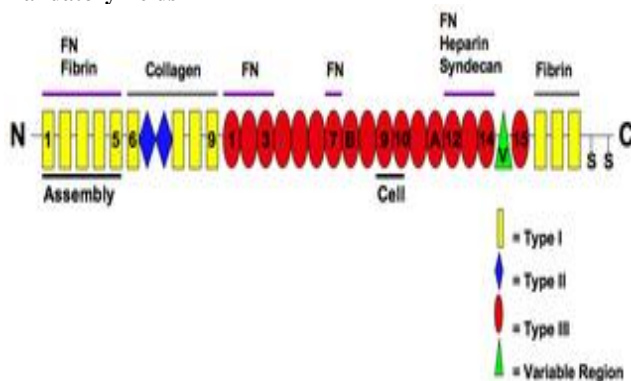
Fibronectin, from the biochemical point of view, is part of the glycoproteins group: heteroproteins are composed by one proteic fraction and one monosaccharide fraction united by a covalent bond. The monosaccharide represents 5% and contains manose, galactose, glucosamine and sialic acid. Fucose and glucose are found in small proportions. These carbohydrates are attached to asparagine remnants. The high molecular weight of carbohydrate has 450 +/-25 kd; the polipeptidic chain of each subunit has an elongated structure of 60-70 nm in length and 2-3 nm in thickness. The role of the carbohydrate molecule is to protect against the enzymatic hydrolysis of FN. (1) Glycoproteins are generally stable to heat, soluble in water and saline solutions at a neutral pH, ethanol precipitable and hard to precipitate with the trichloroacetic acid. FN, under its unreduced form, contains 1-2 groups free SH on subunit and over 22 disulphuric

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intracatenary links. Fibronectin is a ligand for fibrin, chondroitin sulfate, heparin, collagen, and for many of integrines receptors mediating a wide variety of cellular signalling pathways. Each chain has the same linear series of areas (figure no. 1).

Figure no. 1. Modular structure of fibronectin with mandatory fields



ROLE OF FIBRONECTIN IN THE PATHOLOGIC PROCESSES

1. Role of fibronectin in cancer

Plasma and tissue fibronectin are extensively studied in neoplastic processes at various sites, as they evidence both decreases and increases in values. Changes in plasma FN in cancer stem are the result both of the hepatic synthesis change, endothelial, macrophage, and/or coagulation disorders, and the direct involvement of FN in the growth, differentiation, cell migration and metastasis of the malignant melanoma. In malignant melanoma treated with immunostimulants (BCG) some authors (1) have found elevated plasma FN compared to untreated cases. FN could be increased in tumour cells, with its consequent release and a monocyte-macrophage system response with increased synthesis of FN.

In colon and liver cancer, there have been low values in liver metastases. FN; in hepatic metastasis, FN values being obviously increased. Bronchopulmonary cancer, as the primary tumour, leads to increased plasma FN, while lung secondary determinations highlight the decline of its values. Changes of plasma concentration of FN depending on the stage of the colon, liver, brochopulmonary tumour, of the followed treatment or of the presence of metastasis, degree of tumour invasiveness, have led to the theory of organ specificity in interpreting plasma FN values.

Other authors (2) have initiated the theory of cancer treatment by involving FN as a support for chemotherapy, by the therapy with synthetic peptides therapy that block the receptors for functional FN in metastases, fibronectin being selective at the level of the tumour.

2. The role of fibronectin in aterogenesis

It is shown that fibronectin links to the plasma lipoproteins, HDL (high density lipoproteins), LDL (Low Density Lipoproteins), which leads to the storage of the aterogene lipoproteins in the vascular wall. Plasma level of FN is in direct correlation with the level of cholesterol and of LDL. FN is diffusely situated in the atheromatous initial lesions and in the fibre plate, while in the advanced atheromatous plaque, FN disappears almost entirely.(4)

3. The role of fibronectin in predicting premature birth

Approximately 1% of all births are premature births, and more than half of the number of perinatal deaths is those of preterm fetals. Prematurity is considered the main cause of long-term morbidity including mental neuro-psyhic retardation, blindness, deafness, seizures, cerebral palsies and non-

neurological disorders, such as pulmonary dysplasia bronho-and retinopathy of prematurity.

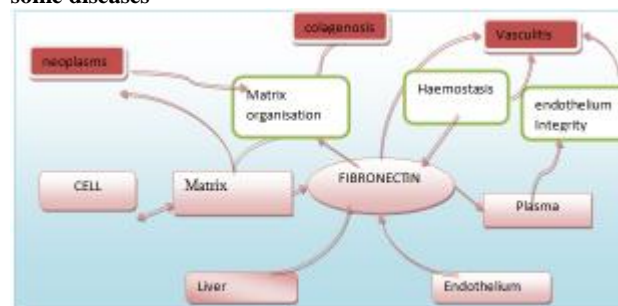
Literature by many studies, included among the biochemical tests, the determination of human fibronectin in serum, plasma, cervical-vaginal secretions and amniotic fluid.

The importance of the predictive factors in causing premature birth leads to the diagnosis conduct and to the therapeutic strategy for the delivery. Fibronectin value in predicting premature birth shall be determined by the sensitivity and specificity of the method but also by positive or negative value. **Fetal Fibronectin** is a glycoprotein produced by fetal cells, at the interface of the corion and the decidua – the fetal test measures the levels of fetal fibronectin of vaginal secretion of the pregnant women between 22-35 weeks of pregnancy: the result is read in less than one hour using the ELISA method. Positive values of fetal fibronectin may indicate that premature birth is not triggered soon, instead of the negative values, which means premature birth can be triggered in the next 7-10 days. The test may be repeated weekly for the category of increased risk for preterm delivery. Negative tests of fetal fibronectin determine a probability of approximately 95% of the non-preterm delivery within the next 2 weeks.(5)

Honest et al, (5) in a comprehensive study, carried out on a very large number of publications and articles (citations 30.076), appeared in medical literature during 1973-2001, have determined the accuracy of fibronectin fetal tests in predicting premature birth. The study included a number of 64 articles consisting of 28 studies on pregnant without symptoms of premature birth and 40 studies on pregnant women with symptoms of premature birth. There were 26876 women included in the study. In conclusion, the determination of fetal fibronectin in vaginal secretion is more accurate in predicting spontaneous premature birth up to 7-10 days after the test on women with symptoms of premature birth risk than the use of the classic parameter-the cervical dilatation.

Some authors (6) have studied the correlation between plasma fibronectin level, body mass index (BMI), average blood pressure, gestational age in weeks and the biochemical parameters: total protein, urea and creatinine serum-all these parameters are risk factors for preeclampsia. The results of this study showed that increasing values of serum fibronectin is connected with obesity, pregnant women in 18-24 weeks with excess weight being at higher risk of preeclampsia than pregnant women with weight corresponding to the age pregnancy. Increased blood pressure in obese pregnant women may result by reducing placental perfusion and increased vascular destruction, with increased synthesis and release of fibronectin and proinflammatory products. Inflammatory lesions are known in medical literature as a pathology with considerably increased plasma values of fibronectin.(1,7,8)

Figure no. 2. The molecular behaviour of fibronectin in some diseases



4. The role of fibronectin in metabolic deases

Obesity, even outside pregnancy has been studied and is associated by most authors with increased values of FN in both plasma and tissue. There have been shown increased values of plasma FN in obesity (1,10), FN concentration being correlated with the insulin level, cortisone and other hormonal substances. Hyperthyroidism, characterized by excess thyroid hormones T3 and T4, causes increased catabolism of FN and the release from the conjunctive tissue, with elevated values in plasma. Determination of plasma fibronectin in diabetic patients highlights its growth by the lowering ability of fibronectin to bind to collagen and heparin, after glycosylation with the perturbation of the extracellular and vascular matrix integrity.

Conclusions

Human fibronectin may be a parameter of prediction, diagnosis, evolution even of monitoring the treatment of premature birth by dynamics dosing and a proper interpretation of the values, knowing the molecular behaviour.

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