EVALUATION OF FIBRONECTIN IN DIABETIC PREGNANCY

THESIS
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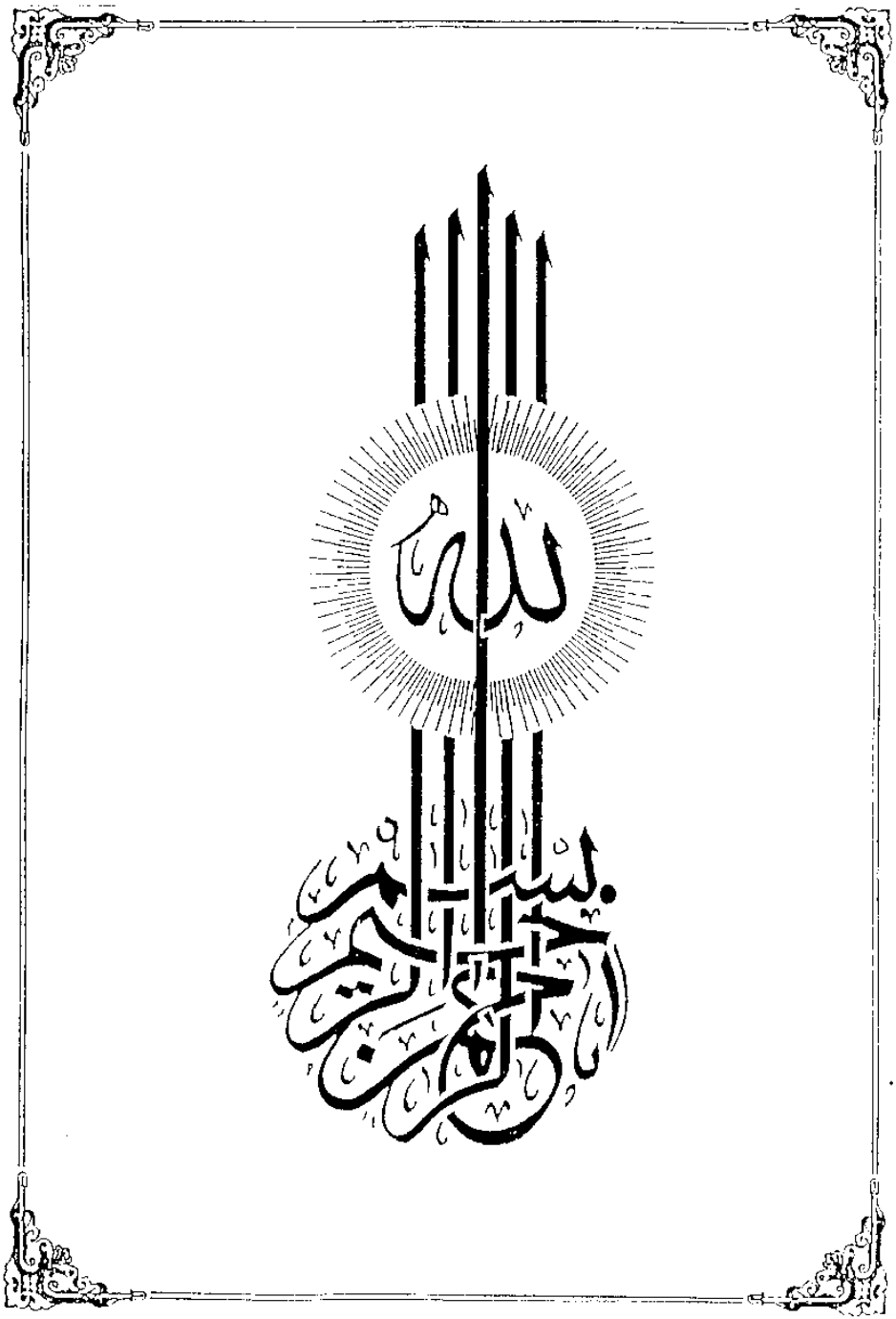

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INTRODUCTION

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Fibronectin is a glycoprotein with a molecular weight 450.000. It is composed of 2 apparently identical subunits which are held together with disulphide bonds.

Fibronectin which is a normal constituent of plasma is also widely deposited in connective tissues, blood vessel walls, basement membranes being a major non collagenous component of all organ stroma (Stathakis et al., 1981).

Fibronectin promotes the adhesion of fibroblasts and macrophages to collagen and seems to play a role as an opsonin for th reticuloendothelial clearance of particles. Fibronectin interactions with heparin fibrinogen, collagen "in particular denatured collagen" and cell surfaces may explain some of its biological activities" (Eriksson et al., 1982).

Fibronectin is increased in case of vascular endothelial damage (Stubb et al., 1984) elevated fibronectin may antagonise clotting by enhancing fibrinolysis aiding in endothelial repair and solubilising the fibrin monomer thereby preventing the formation of the fibrin net work. Fibronectin also acts as an opsonin, allowing phagocytosis of formed blood clots by macrophage from microcirculation (Kaplan, 1984).

Management of the pregnant women with diabetes continues to present a challange to the physician, obstetrician and pediatrician. In spite of the marked improvement in perinatal mortality yet most centers report a ten fold increase above general population (Beard and Maresh, 1988).

It has been repeatedly shown that fibronectin is increased in diabetic patient with various form of vasculopathy (Nardelle et al., 1987).

At least a part of fetal complications during pregnancy may be related to the degree of vascular affection and accordingly it seems logic to study fibronectin level during the course of diabetic pregnancy in an attempt to predict the fetal outcome.

AIM OF THE WORK

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The aim of this work is to evaluate the possible use of fibronectin as a marker of fetal well being and outcome of diabetic pregnancy.

REVIEW OF LITERATURE

Review of literature

Historical Perspective

The term fibronectin describes a family of structurally and immunolojically related high molecular weight glycoproteins that are present throughout the body. Two forms of fibronectin have been characterized, a soluble form in blood and other body fluids and another insoluble form is present on surfaces of cells, in extracellular spaces of connective tissue and as a component of basement membrane (Mosesson and Amarani 1980 , Ruoslahti et al 1981).

The first fibronectin to be isolated was partially purified from human plasma by Morrison et al "1948". They described a protein component of fibrinogen containing fraction that was cold insoluble, and present in the precipitate that forms when plasma stands in the cold hence the earlier name "cold insoluble globulin or CIg. Edsall et al 1955 gave strong indications that the molecule of the cold insoluble slobulin was large and suggested that it was a dimer composed of 2 fibrinogen molecules.

Shortly thereafter Smith and Von korff 1957 isolated and described a fraction of human plasma which is characterized by cold insolubility in the presence of heparin. In ultracentri- fugation two components were found the major fraction resembling fibrinogen while the minor one resembling cold insoluble globulin. Later on, the cold insoluble globulin was isolated and highly purified as an unique and major plasma protein by (Mosesson and Umfleet) 1970. They proved by immunochemical electrophoretic studies that cold insoluble globulin was not a form of fibrinogen. This differed from the view of Edsall et al 1955. The cellular form of fibronectin was discovered and purified from fibroblasts in the early 1970. During that time a number of investigation had been directed towards a protein associated with the surface of fibroblast grown in culture and was frequently lost or transformation by oncogenic viruses "Yamada and Weston 1974"

This term is now becoming widely accepted in reference to a variety of proteins independently examined and designed by different terms. For example the plasma soluble form of the protein has been called opsonic alpha$_2$ glycoprotein "Blumenstock et al 1978". cold insoluble globulin "Morrison et al 1948 as well as plusma fibronectin "Ruoslahti et al 1981". The insoluble tissue associated fibronectin has been called large external transformation sensitive

protein "LETS" Hynes 1973, cell surface protein C.S.P. Yamada and Weston 1974 soluble fibroblast antigen SF-antigen Ruoslahti and Vaheri 1974 cell attachment ar adhesion factor "Klebe 1974 and Pearlstein 1976) .Galaccoprocein, antigelatin factor "Gahmberg et al 1974" Zeta protein (Blumberg and Robbins 1975) cell spreading factor Grinnell 1976 as well as cellular fibronectin (Ruoslahti et al 1981) The work done by Ruoslahti and Vaheri 1975 indicated that cold insoluble globulin was antigenically identical to large external transformation sensitive protein. This brought to light that fibronectin exists as a tissue and a blood protein.

Biological Functions of fibronectin

(Mosesson et al 1980)

Cell cell aggregation

. Agglutinates fixed erythrocytes

. Aggregates liver cells

. Binds to fixed and live bacteria

Cell substratum adhesion

. Mediates cell attachment to collagen fibrin and plastic substrate promotes cell spreading

Reversion of transformed phenotype

. Promotes cell alignment and decreases over lapping

. Restores normal surface morphology

. Restores fibroblastic morphology

. Promotes microfilament bundle organization.

Increases cell Motility

Stimulates reticuloendothelial clearance of particles

. Liver cell binding

. Uptake by macrophages in culture

Binds to specific macromolecules

. Actin	. Cell surface receptors
. Collagen and elastin	. Dextran sulfate
. DNA	. Fibrin & fibrinogen
. Gangliosides	. Haparan sulfate
. Heparin	. Hyaluronic acid
. Staphylococcus aureus	. Transglutaminase, factor XIIIa

Role of fibronectin in cell attachment

Yamada and olden 1978 suggested that fibronectin might perform an adhesive function. It agglutinates formalinized sheep erythrocytes (Yamada et al 1975) and becomes incorporated into the clot in blood coagulation (Mosher 1975) which may be important in providing a favorable attachment matrix for the cells that grow into the clot "Ruoslahti et al 1981) The addition of fibronectin to cell culture promotes odhesion of cells to substratum "Pearlstein 1976" plasma and cell surface fibronectins are equally

active in this respect "Yamada and kennedy 1979". Observations in vitro may not accurately reflect findings in vivo. Anti fibronectin antiserum produces only 60% inhibition of adhesion to fibronectin covered subendothelial matrices in vivo, as opposed to 100% in vitro "Pearlstein and Hoffstein 1981" It is some what paradoxical that fibronectin despite of its cell attachment enhancing properties promotes motility of cells "Ali and Hynes 1978".

Normal human cells are rich in surface fibronectin and are able to spread in the absence of exoqenous fibronectin. Virus transformed cells and cells of neoplastic origin have either reduced or no surface fibronectin and are dependent on serum or plasma for spreading "Rajaraman et al 1983".

Role of fibronectin in Differentiation

Fibronectin appears early in development and seems to be abundant in embryonic tissues. Fibronectin is first detected in the differentiation of the endoderm and is found, in the mesoderm but not in the differentiated ectoderm "Vaheri et al 1985). Several lines of evidence suqqest that fibronectin plays a role in directing differentiation and morphogenetic movement "Ruoslahti et al 1981".