PLASMA FIBRONECTIN IN PREGNANCY INDUCED HYPERTENSION

THESIS

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BY

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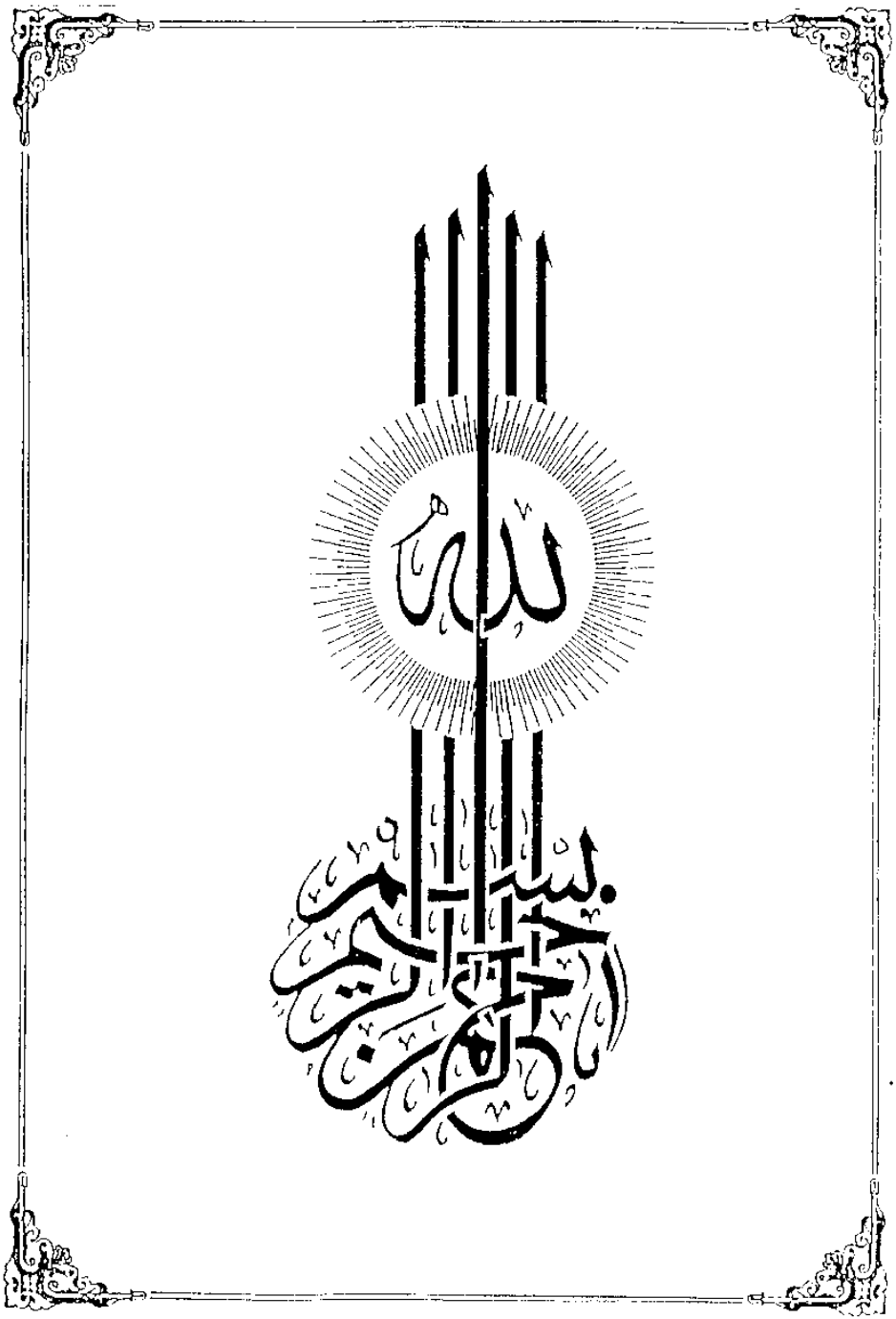

DEDICATION

To My Family

With Love...

CONTENTS

INTRODUCTION

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Fibronectins are high molecular weight glycoproteins (450 kilo daltons), which have been classified as α_2-globulins, and are present in many tissues and in most body fluids (Pearlstein et al., 1981). Fibronectin was first identified in the 1940s (Morrison et al, 1948), and isolated from plasma in 1970 (Mosesson and Umfleet, 1970).

There are at least two forms of fibronectin. The soluble form, usually referred to as plasma fibronectin, is present at a rather high concentration (200-400 Ug/ml) in plasma, and results primarily from synthesis by the vascular endothelium, and also by hepatocytes (Graninger et al., 1985). The insoluble form, called cellular or tissue fibronectin is produced by fibroblasts, endothelial cells, macrophages, and blood platelets and is a wide-spread component of connective tissue and basement membranes (Saba and Jaffe, 1980).

A variety of functions have been ascribed to fibronectin, inducing roles in opsonization, cell adhesion, cell motility, tissue repair, and coagulation (Mosher, 1984).

Abnormalities of the vascular endothelium have long been suspected to have a pathophysiologic role in preeclampsia. Decidual vascular endothelial lesions, glomerular endotheliosis, and platelet consumption are known to accompany many cases of preeclampsia (Pritchard et al., 1976).

Fibronectin is intimately associated with the vascular endothelial basement membrane, and increased levels of fibronectin in plasma have been observed in established gestational proteinuric hypertension or pregnancy induced hypertension (Stubbs et al., 1984; Lazarachick et al., 1986; Erisken et al., 1987; Saleh et al., 1987; Thurnau et al., 1987; Lenoardi et al., 1988 and Ballegeer et al., 1989).

AIM OF THE WORK

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The first objective of the present study is to review the literature about the changes in plasma fibronectin occuring in cases of pregnancy induced hypertension (PIH).

The second objective is to determine the plasma fibronectin level in pregnancies complicated by PIH, and compare it to its level in normal pregnancy.

The thrid objective is to find out any possible relation between changes in plasma fibronectin level and the severity of PIH.

REVIEW OF LITERATURE

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Fibronectin

I. Definition and Nomenclature

The term Fibronectin describes a family of structurally and immunologically related high molecular weight glycoproteins that are present in blood and other body fluids, also existing on many cell surfaces, in extracellular fluids, in connective tissues and in most basement membranes (Mosesson and Amrani, 1980).

This protein was known by many other names including cold insoluble globulin (Morrison et al., 1948), antigelatin factor (Wolff et al., 1967), opsonic protein (Saba, 1970), large external transformation sensitive protein (Hynes and Bye, 1974), soluble fibroblast antigen (Ruoslahti and Vaheri, 1974) cell surface protein (Yamada and Weston, 1974) cell surface factor (Pearlstein, 1976), and lastly cell spreading factor (Grinnell, 1976).

Now, there is general acceptance of the term fibronectin, which was created to emphasize the propensity of the protein to bind to fibrous proteins like collagen and fibrin (Fibra, Fibre and necture, to bind) (Mosesson and Amrani, 1980).

II. Historical Background

Fibronectin was reported for the first time by Morrison et al. (1948), who described a protein component of fibrinogen containing a fraction, that was cold insoluble. Unlike fibrinogen it was not thrombin coagulable. It had a more rapid anodal electrophoretic migration rate and higher sedimentation coefficient than did fibrinogen.

Later, physicochemical analysis reported by Edsall et al. (1955) led to the suggestion that cold insoluble globulin (CIg) was a modified dimer of fibrinogen. In 1957, Smith and Von Kroff discovered a protein in heparin-induced cold precipitate plasma that had properties similar to those of the CIg.

In 1968, Mosesson et al. investigated patients with chronic intravascular coagulation secondary to an occult neoplasm. The illness was characterized by the persistence of cold induced plasma precipitate termed "Cryofibrinogen". The solubilized cryofibrinogen was partially coagulable by thrombin, thus proving that fibinogen was present.

Follow up investigations by Mosesson and UmFleet in 1970 presented a method for isolation and purification of cold insoluble globulin and provided clear evidence that it was a unique and major plasma protein with a normal concentration of 200-400 Ug/ml.

In the early 1970s, a number of investigations focussed on the changes that occured in cell surface proteins of fibroblasts as a consequence of transformation by oncogenic viruses. Particular attention was paid to a large external transformation sensitive glycoprotein (LETS) that was released from the fibroblast cell surface into the culture medium (Hynes and Bye, 1974; Yamada and Weston, 1974; Gahmber et al., 1974 and Blumberg and Robbins, 1975).

Rouslahti and Vaheri (1975) reported that cold insoluble globulin was antigenically identical to LETS, this brought to light the uniqueness of fibronectin as both a cell surface/matrix protein and a blood protein.

In addition, Saba et al. (1978 a), purified the serum protein termed α_2 surface-binding glycoprotein which is considered as an opsonic agent and have shown it to be immunochemically identical and structurally very similar to CIg.

III. Physiology and Biochemistry

1. Synthesis and Distribution

Fibronectin is found in two forms. An insoluble one present in connective tissue, blood vessel walls and basement membranes. The second is a soluble form present in plasma and extracellular fluids including amniotic fluid and cerebrospinal fluid (Mosesson and Amrani, 1980).

Immunofluorescent studies of normal tissue have demonstrated that it is present in many basement membranes, around smooth muscle cells, in sarcolemma of striated muscle fibres, in the sinusoidal walls of the liver, stroma of lymphatic tissue and in loose connective tissue (Stenman and Vaheri, 1978).

Circulating fibronectin results form synthesis by hepatocytes and vascular endothelial cells (Stubbs, T.M. et al., 1984). However, synthesis of fibronectin has been demonstrated in culture for a large number of cell types including fibroblasts; vascular and cornecal endothelial cells; astroglial cells; Schwann cells; glomerular cells; intestinal, breast, kidney and liver epithelial cells; hepatocytes; chondrocytes; myoblasts; macrophages and certain epithelial cells including those derived from carcinoma cell lines, also peritoneal macrophages (Jaffe and Mosher, 1978; Oberly et al., 1979; Mosesson and Amrani, 1980 and Saba et al., 1986 a).

During embryogenesis, fibronectin is first detectable on cells of the blastula inner cell mass (Zetter and Martin, 1978). At later developmental phases, fibronectin is lost or becomes redistributed concomitant with differentiation of mesenchymal cells into muscles, cartilage and renal tubular epithelium (Chen L.B., 1977).