COAGULATION DEFECTS IN TOXAEMIA OF PREGNANCY

(Pre-eclampsia)

Thesis

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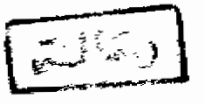

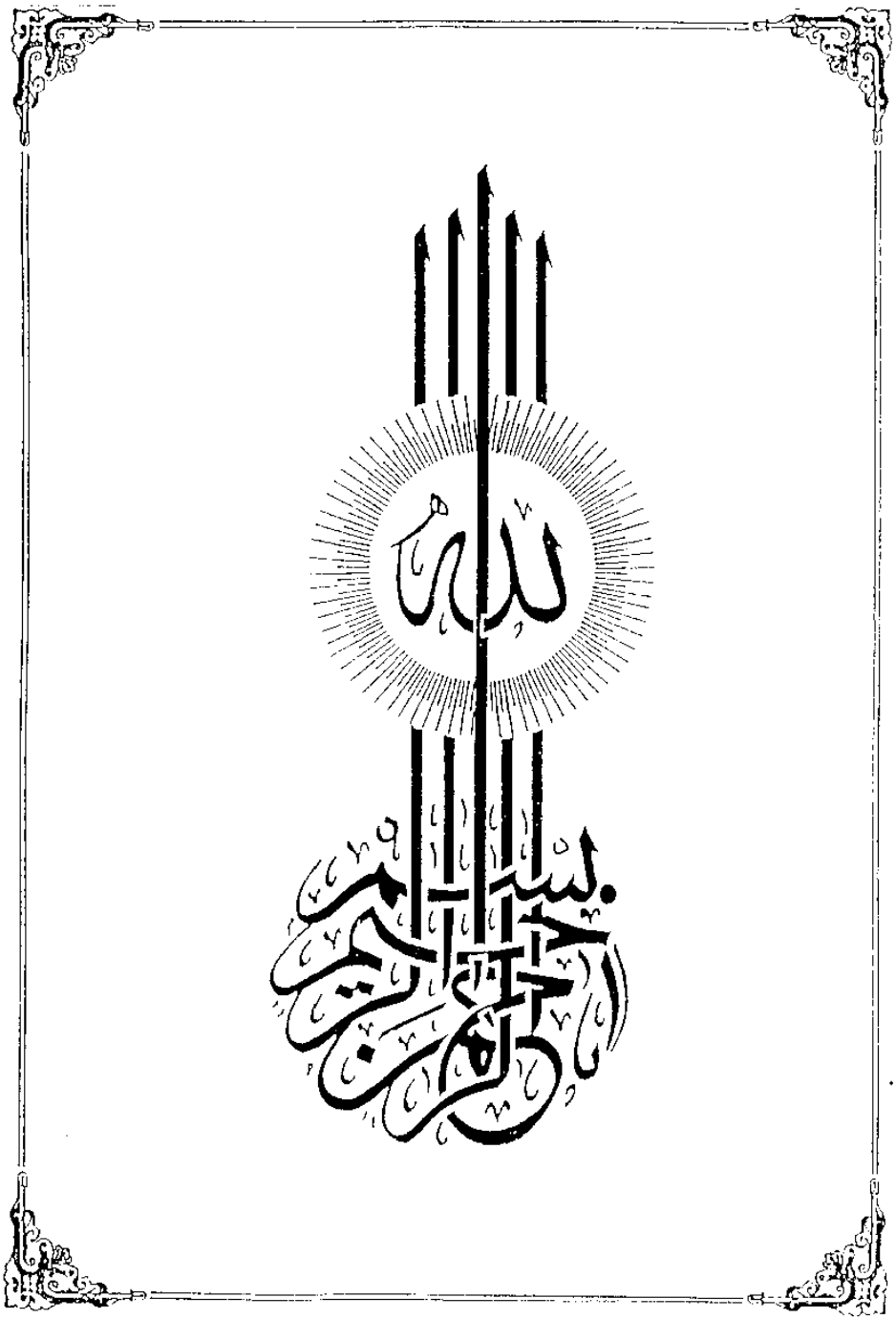

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CONTENTS

PREGNANCY INDUCED HYPERTENSION

In 1893 Georg Schmorl described in women who had died following eclampsia, anemic and hemorrhagic necrosis with the deposition of fibrin network in the periportal areas of the liver, in association with small thrombi in the interlaboular veins. Furthermore, thrombi were found in the glomerular capillaries and, although less frequently, in the brain. By 1901 Schmorl had extended his material to 73 cases, in 71 of which the typical periportal lesions of the liver were seen. He concluded that" there existed a typical anatomical substrate in eclampsia, and that in eclampsia a typical change in the blood occurred, which manifested itself in multiple thrombus formation " . Schmorl's findings were confirmed, half a century later, by McKay, et al. (1953).

Vassali, et al. (1963) , by using immunofluorescent technique, demonstrated in kidney biopsies of preeclamptic patients the deposition of fibrinogen or fibrin or one of its immunologic derivatives within or underneath the endothelial cells of glomeruli.

Arias and Mancilla-Jimenez (1976) demonstrated

with a smililar technique applied to liver biopsies,the deposition of fibrin (ogen) in the periportal areas.

Stahnke described in 1922 the association of eclampsia and thrombocytopenia. Pritchard , et al. (1954) described three cases of eclampsia, two of them fatal, with severe thrombocytopenia and in addition, a prolonged thrombin time, a prolongation of bleeding time, and evidence of hemolysis. Bonnar, et al. (1971) described increased serum levels of fibrin (or fibrinogen) degradation products. Pritchard, et al. (1976),in a large group of eclamptic patients, found thrombocytopenia to be present in 29%,raised fibrinogen degradation products in only 3% , and a positive fibrin monomer test in only 5% .

Due to the development of new techniques, convincing evidence is now provided that the coagulation system is activated in preeclampsia (Weenink , et al., 1985) .

Following a single oral dose of acetyl salicylic acid, platelets irreversibly lose their ability to synthetize endoperoxides upon stimulation with thrombin or arachidonic acid. This may be measured as a decreased production of

malondialdehyde (MDA) , a stable end product of endo-peroxide synthesis. The time required for malondialdehyde values to return to baseline levels reflects platelet production, which is inversely related to platelet life span. With this method it was confirmed that in normal pregnancy platelet life span is normal. However, in pre-eclamptic patients platelet life span is shortened : 5.1 $\pm$ 0.34 days versus 8.9 $\pm$ 0.24 days in normal pregnancy (Wallenburg and van Kessel , 1978 , and Rokoczi, et al., 1979).

Increased β-thromboglobulin plasma levels may reflect increased platelet activation or platelet turnover .Increased plasma β-thromboglobulin levels have been demonstrated in pre-eclampsia. This may be due to increased platelet turnover in the circulation. However, decreased kidney function in pre-eclampsia may contribute to increased plasma B-thromboglobulin levels because renal excretion is the main mechanism of β-thromboglobulin clearance(Redman, et al., 1977 , and Douglas, et al., 1981) .

Socol, et al. (1984) have demonstrated a strong correlation between elevated β-thromboglobulin and reduced

creatinine clearance in women with pre-eclampsia .

Whigham, et al. (1978) , found decreased platelet aggregation in response to aggregating agents and lower platelet serotonin levels. These findings suggest that circulating platelets in pre-eclampsia have undergone reversible aggregation and partial release.

Research in the role of prostaglandins in vascular disease has renewed the interest in platelets and their significance in pathogenesis of the pre-eclampsia - eclampsia syndrome. Prostacyclin, produced by the vessel wall, is a powerful vasodilator and inhibitor of platelet aggregation. The physiological counterpart thromboxane A_2 is produced by the platelets and is a powerful aggregating agent and vasoconstrictor. There is decreased prostacyclin production in vessels obtained from pre-eclamptic patients(Bussolino, et al., 1980) . More recent studies have documented an increase in thromboxane A_2 in women with pre-eclampsia (Matensson and Wallenburg, 1984) .

It has been suggested that the disturbed prostacyclin-thromboxane A_2 balance might be responsible for the occurence

of vasoconstriction, enhanced platelet activation, and invivo platelet aggregation and fibrin deposition(Weenink, et al., 1985).

Thrombin acts on fibrinogen, by cleaving fibrinopeptides A and B , a process which is followed by fibrin monomer formation. Fibrinopeptide A levels measured by radioimmunoassay, have been reported to be five times higher in pre-eclamptic patients (Weiner, et al., 1983).

Fibrin monomers polymerize with fibrinogen to form soluble fibrinogen /fibrin complexes. In pre-eclampsia the mean complex concentration, measured by column chromatography , has been reported to be three times higher than in normal pregnancy(McKillop, et al., 1976) .

When thrombin acts on factor VIII, factor VIII procoagulant activity(VIIIc) decreases, without a concomitant decrease of the factor VIII-related antigen(VIII RA). Thus , an increased ratio of factor VIII RA to factor VIIIc is a possible index of thrombin generation. This ratio is increased in pre-eclampsia(Thornoton and Bonnar, 1977) .

Kuypers found that the mean ^{125}I fibrinogen half-life in 12 normotensive third-trimester pregnant women was 78.7 hours . In 11 patients with mild pre-eclampsia, the mean ^{125}I-fibrinogen half-life was significantly shortened to 49.5 hours. Fibrinogen levels in both groups did not differ . After subcutaneous heparin treatment the fibrinogen half-life returned to normal, indicating that the increased fibrinogen turnover was thrombin-mediated (Weenink, et al., 1985) .

Antithrombin lll , a protein synthesized by the liver and endothelial cells, is considered to be the main physiologic inhibitor of blood coagulation. It forms irreversible complexes with activated clotting enzymes, notably with factor X_a and thrombin . These complexes are subsequently cleared by the reticuloendothelial system. Decreased antithrombin III levels, either of hereditary or acquired origin are associated with an increased risk of thromboembolism. Antithrombin III levels are not depressed in normal pregnancy, although a small decrease may occur at term. In pre-eclampsia, a significant decrease in antithrombin III levels occurs(Weiner and Brandt, 1982 , and Weenink, et al.,1983).

This decrease is not observed in gravidas with pre-existent hypertension without superimposed pre-eclampsia, even when pre-existent proteinurea due to chronic renal disease is present. Low antithrombin III levels correlate with the degree of maternal morbidity. In addition , low antithrombin III levels correlated with placental infarction and poor fetal outcome(Weenink, et al., 1984) .

BLOOD COAGULATION

Blood coagulation is an end result of a cybernetic system in which the control components consist of positive and negative feedback ,equflibria, controlled chain reaction , multiple enzyme involvement, apparent stoichiometric reactions, and integration with organ function(Seegers,1976).

In 1835 the Scottish physiologist Buchanan likened the process of coagulation to the curdling of milk, the first suggestion that coagulation was an enzymatic process (Brandt, 1985). During the last quarter of the nineteenth century Schmidt (1876) discovered that the clotting of blood may generally be due to an enzyme called thrombin, and that thrombin clots fibrinogen in the presence of neutral salts.

The classic theory of blood coagulation proposed by Morawitz (1905) assumes the interaction of four plasma components namely; prothrombin, thromboplastin,thrombin, and fibrinogen. Ionized calcium is required for the basic reactions, which may be outlined as follows:

I. Prothrombin + Calcium ion + Thromboplastin ⟶ Thrombin.

II. Fibrinogen + Thrombin ⟶ Fibrin.

In 1964 , two essentially identical mechanisms termed a waterfall and a cascade were suggested to explain the enzymatic nature of blood coagulation in the intrinsic pathway. According to these concepts, protein clotting factors interact with each other in a stepwise manner in which one acts as an enzyme and the other as a substrate. Accordingly, a sequence of reactions was visualised which eventually lead to the formation of thrombin (Davie and Ratnoff, 1964 , Macfarlane, 1964) . The classic theory had to be modified to include the newly discovered factors, the number of which increased rapidly for a time.

With the exception of factor XIII, each of the coagulation enzymes is a serine protease . This large family of enzymes also includes trypsin, chymotrypsin, and plasmin. Serine proteases function by cleaving selected peptide bonds in specific substrate proteins. They are characterised by having a serine residue at their active site (Hutton1981).

The numerical system for identifying accepted coagulation factors proposed by Koller has since been recommended for universal use by the International Committee for the