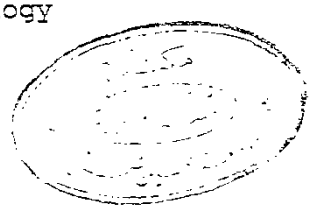
A STUDY ON COAGULATION DEFECTS IN ABRUPTIO PLACENTAE

Thesis submitted for the partial fullfilment of the
M. D. of Obstetrics and Gynaecology



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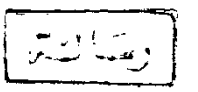

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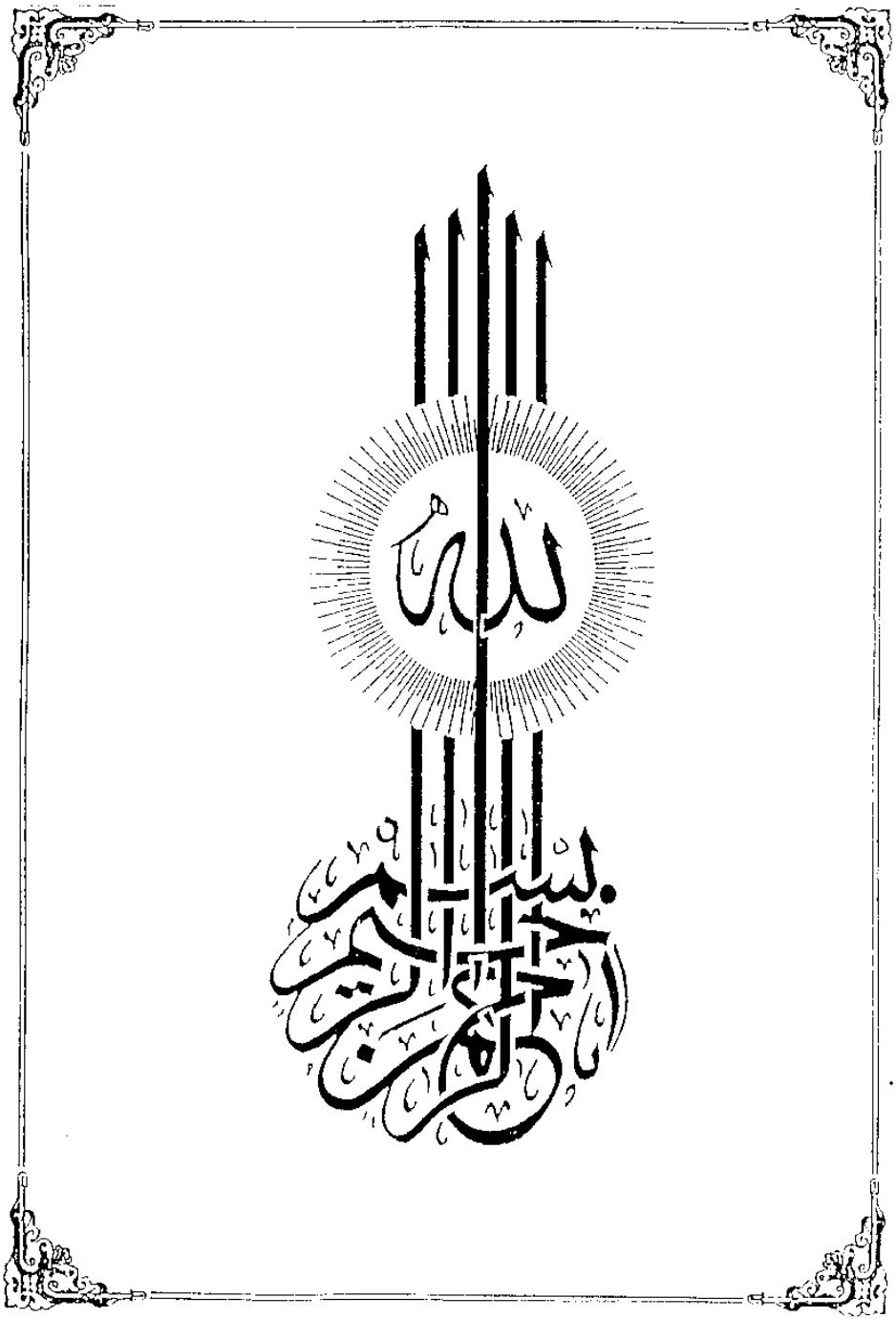

DEDICATION

I would like to express my deep gratitude and thanks to Professor Dr. ***KHALIL EL LAMAY****, Professor of Obstetrics and Gynaecology, Ain Shams University, for his kind and energetic help in this work to ensure that it would reach an updated level.*

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The most common cause of consumptive coagulopathy in pregnancy is placental abruption. Overt hypofibrinogenemia (less than 150 mg per 100 ml of plasma) along with elevated levels of fibrin-fibrinogen degradation products (F.F.D.P.s), variable decrease in other coagulation factors and manifestations of bleeding disorders occur in about 30% of cases with abruption severe enough to kill the fetus. Such coagulation defects are found very much less often in cases in which the fetus survives (Robert and Maria, 1986).

The major mechanism in the genesis of the coagulation defect of placental abruption almost certainly is the induction of coagulation intravascularly and to a less extent retroplacentally, (Dixon, 1973), as it was found that the amounts of fibrin deposited retroplacentally are insufficient to account for all the fibrinogen missing from the circulation.

In patients with severe abruptio placentae, depletion of factor (II) (Prothrombin), factor (V),

(VIII), anti-thrombin III and severe thrombocytopenia may be present. The release of large amounts of FDPs (Fibrin Degradation Products) into the circulation from the intravascular fibrin has a complex anti-coagulant effect and interferes with the thrombin/fibrinogen reaction, polymerization of fibrin and platelet function.

We were stimulated to study the coagulation abnormalities in severe and mild cases of abruptio placentae and compare them with cases of normal pregnancy during labour as control.

REVIEW OF LITERATURE

CHAPTER I

COAGULATION FACTORS

The major site of synthesis of the coagulation factors is the hepatocyte. Two interesting features are emphasized by Barnhart and Noonan (1973). One is that not all hepatocytes are equally active in synthesizing the various factors. The other is that the feedback mechanism for stimulating synthesis is not a low concentration of the factor as would be achieved by plasma-pheresis but rather products produced when the factor is depleted during the coagulation sequence (Miale, 1977).

The different coagulation factors are:

1. Fibrinogen (Factor I):

Physiology and function of plasma fibrinogen:

Blood coagulation ultimately depends on thrombin catalyzed conversion of fibrinogen to fibrin. It is one of the major plasma proteins and is a main component in haemostatic mechanism, being designated as factor I in the coagulation pathway. Fibrin constitutes the physical basis of all blood clots and provides the framework for the permanent haemostatic plug. Also

fibrinogen may be essential for normal platelet function and wound healing (Wintrobe et al., 1974).

Historical Review:

Fibrinogen may be considered a globin-type protein containing about 3% carbohydrate. The earliest report of the amino acid composition of both human and bovine fibrinogen were based on paper chromatography (Baily, 1944).

More recently automated analysis has been used to determine the amino acid composition of bovine and human fibrinogen (Murray and Huseby, 1967).

The pioneer work in the titration behaviour of highly purified fibrinogen was done by Mihalyi in 1954, who found that 3.6 new alpha-amino groups were released with clotting. This is well recognized today as the proteolytic action of thrombin on fibrinogen.

Hall and Slayter (1959), performed electron microscopic studies and found that the fibrinogen molecule is composed of three spheres linked by a filamentous fiber. Koppel (1970) proposed a spherical model for the molecule.

Later on, Blomback and Blomback (1972) proposed a new model. The molecule of fibrinogen would

be a large sphere containing many molecules of water. This would explain the large size relative to the molecular weight (Hurdy-Clergon et al., 1975).

Biochemistry:

Fibrinogen is a relatively insoluble glycoprotein that contains from 3 to 5% carbohydrate (Wintrobe et al., 1974). Purified preparations that are homogenous by most criteria have been obtained by a number of relatively simple biochemical methods (Collen, 1972). Such purified fibrinogen is 95 to 97% coagulable by thrombin, a figure that approximates the theoretic maximum because 3 to 5% of the molecule is lost as fibrinopeptides during coagulation (Blomback, 1966).

The molecular weight of highly purified fibrinogen is approximately 340,000 Daltons (Hoffbrand and Lewis, 1981).

Electron microscopy has revealed that the fibrinogen molecule is composed of three nodular subunits, 5 to 7 nm in diameter, interconnected by a thin filament about 1.5 nm thick (Hall and Slayter, 1959).

Studies of molecular subunits, suggest that fibrinogen has dimeric structure. Each half of the

molecule contains three identical pairs of polypeptide chains (designed Alpha, Beta and Gamma) with respective molecular weights of 73.000, 60.000 and 50.000 (McKee, 1970).

The two halves of the molecule are connected by three intradimer disulphide bonds and the three chains comprising each half are firmly interconnected by interchain disulphide bonds which are concentrated in the N-terminal end of the molecule (The N-terminal disulphide knots). These disulphide knots appear to be in the central portion of the molecule rather than the lateral nodules, as previously supposed (Blomback, 1969) Fig. 1.

Two pairs of peptides are removed proteolytically from the fibrinogen molecule by the action of thrombin. These have been designated fibrinopeptides A and B, and correspond to the terminal ends of alpha and beta chains. The terminal peptides of the gamma chains are not removed by the action of thrombin. Fibrinopeptide B is chemically homogenous, but two subtypes of peptide A have been isolated (Fibrinopeptides Ay and Ap) (Blomback, 1966).

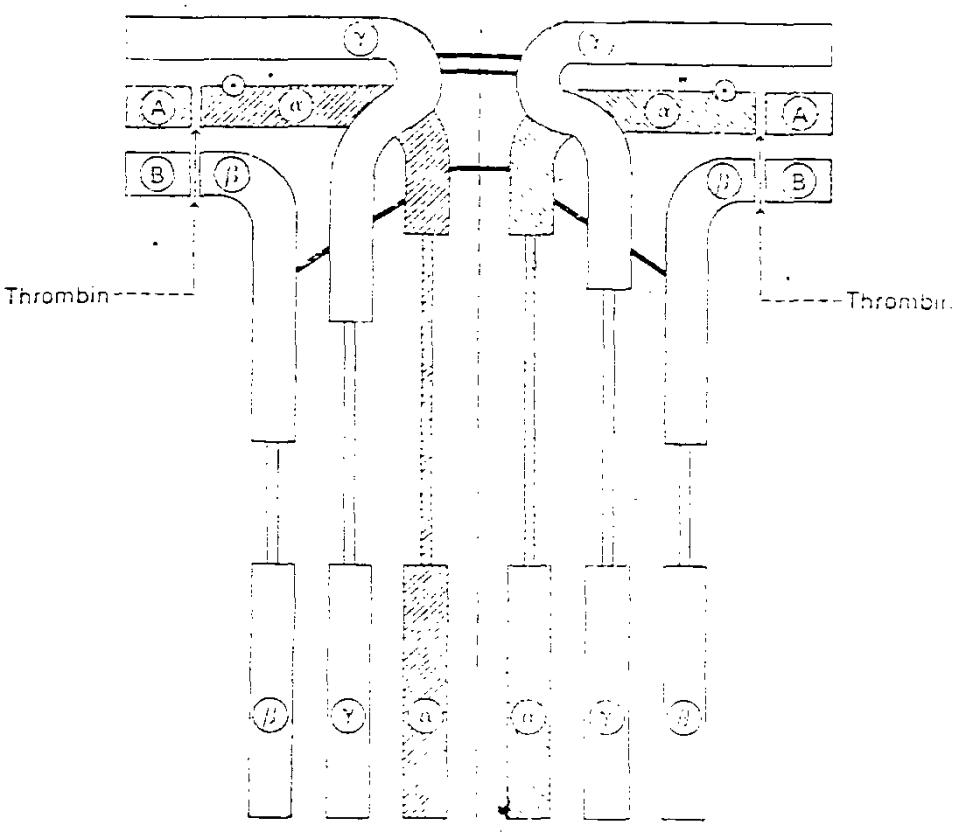

Figure (1)

The molecular structure of the fibrinogen molecule (Blomback, 1969)

Biodynamics:

Fibrinogen is synthesized by the parenchymal cells of the liver. Its concentration in plasma normally ranges between 160 to 415 mg/dl (Chroback, 1967). Fibrinogen is present also in lymph but its amount is less than in plasma.

Extensive studies employing isotopically labelled fibrinogen have revealed that the kinetics of its catabolism are very complicated. The turnover rate of human fibrinogen ranges from 1.7 to 5 g/day (30 to 60 mg/kg/day) (Takada, 1966).

There is indirect evidence that catabolism occurs continuously and may involve the conversion of fibrinogen into soluble derivatives of lower molecular weight, these have been isolated from normal plasma. The in-vivo sites of fibrinogen catabolism are unknown (Harpel and Mosesson, 1972).

There is indirect evidence that plasma levels of fibrinogen degradation products, possibly acting as a "feedback" control may constitute the major regulators of the rate of fibrinogen synthesis. In tissue culture free fatty acids increase fibrinogen synthesis by human liver slices (Wintrobe et al., 1974).