EVALUATION OF PROPHYLAXIS FOR DEEP VENOUS THROMBOSIS WITH SUBCUTANEOUS HEPARIN THERAPY IN HIGH RISK PREGNANCY

THESIS

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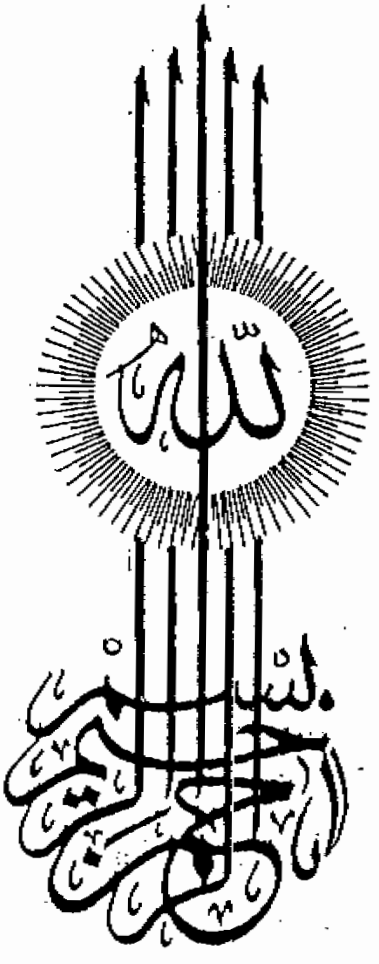

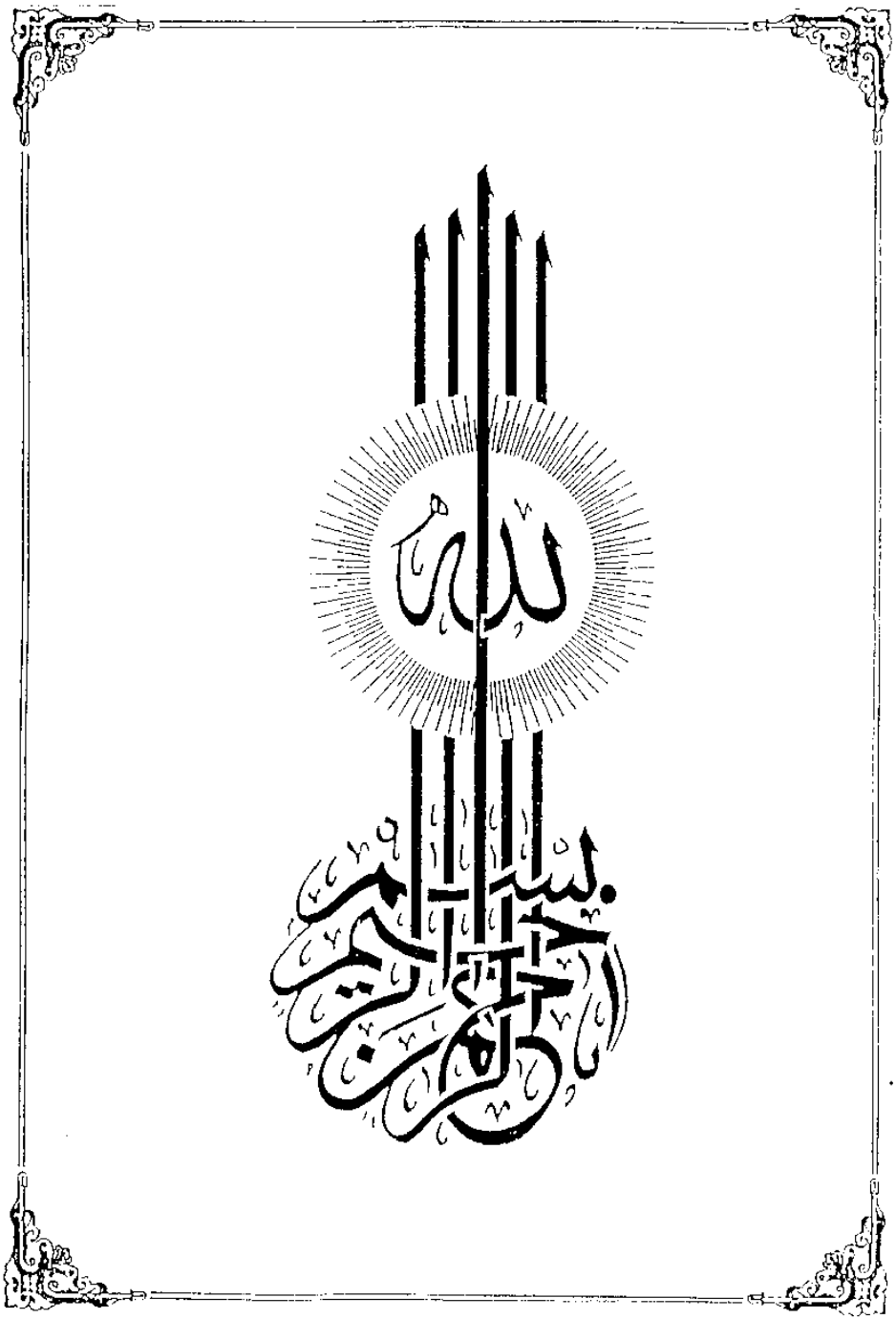

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Introduction & Aim Of The Work

puerperal patients than in antepartum patients by about 3:1. Over 50% of cases appear within the first 3 days but the condition may become manifest at any time up to 4 weeks postportum. Prophylactic therapy is indicated in this group. (Edward J. et.al. 1981).

As fatal pulmonary embolism is sixteen times greater after a Caeserean than after vaginal delivery, so prophylaxsis for deep venous thrombosis inthis group is recommended.

The international multicenteral trial held by V.V. Kakar et.al. in 1975 gave a result that a standard regimen of 5000 units of Heparin given two hours before operation and eight-hourly thereafter fulfills most of the criteria, demanded of an ideal prophylactic agent. It prevents postoperative fatal pulmonary embolism. It is well tolerated by the patients; it requires no laboratory control to regulate dosage; and it does not produce serious bleeding when the patient undergoes major surgery. This form of prophylaxis against venous thrombo-embolism can be recommended for use on a large scale in high risk patients undergoing major surgery.

Application of Kakar's regime to high risk pregnant ladies to prevent venous thrombo-embolism have been tried in this work and its results have been evaluated.

Aim of the Work

As in our facilities, the methods of early detection of subclinical thrombosis are not available, hence, prophylaxis is important.

The Aim of this study is to asses the safty and efficacy of subcutaneous low dose Heparin prophylaxis according to Kakkar's regime (1973,1975).

Review Of Literature

COAGULATION FACTORS

Table 1 &

PREGNANCY INDUCED

CHANGES

Factor		*Chemical characteristics*	*Production*	*Normal plasma levels*	*Change in normal pregnancy*
I	Fibrinogen	Glycoprotein MW = 340 000 3 subunits	Liver	2 – 4 g/l	Increase to 6 or 8 g/l in 3rd trimester, ↓ after delivery
II	Prothrombin	Glycoprotein MW = 6900	Liver, vitamin K dependent	75 – 125%	No change. 100 – 125%
IV	Calcium			4.7 – 5.6 mEq/1	
V		? lipoprotein MW>200 000	Liver	75 – 125%	↓ after delivery, normal by 1 week (100 – 150%)
VII		Glycoprotein MW = 48 – 100 000 α or β globulin	Liver, vitamin K dependent	75 – 125%	Progressive increase during pregnancy. (150 – 250%)
VIII		Lipoglycoprotein MW>2 000 000 α or β globulin	Endothelium, liver	75 – 150%	200 – 600%
IX		Glycoprotein MW = 50 – 100 000 α or β globulin	Liver, vitamin K dependent	75 – 125%	100 – 150%
X		Glycoprotein MW = 50 – 100 000 α globulin	Liver, vitamin K	75 – 125%	100 – 250%
XI		β or γ globulin MW = 50 – 200 000	Liver	75 – 125%	↓ in pregnancy (50 – 100%)
XII		β or γ globulin MW = 80 000	Unknown	75 – 125%	100 – 200%
XIII		a_2 globulin MW = 32 000 4 subunits	Liver	75 – 125%	↓ in pregnancy. (35 – 75%)

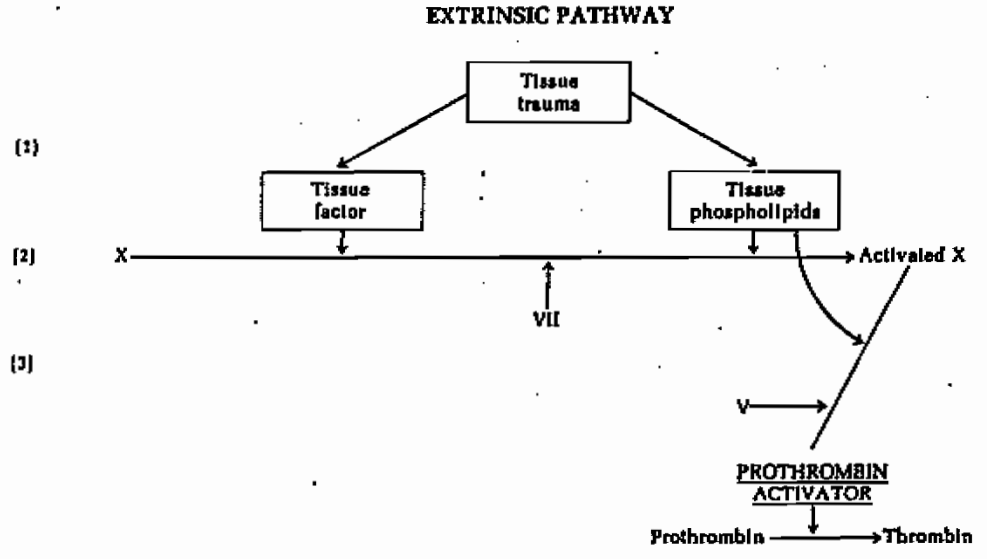

Fig. 1 The extrinsic pathway for initiating blood clotting.

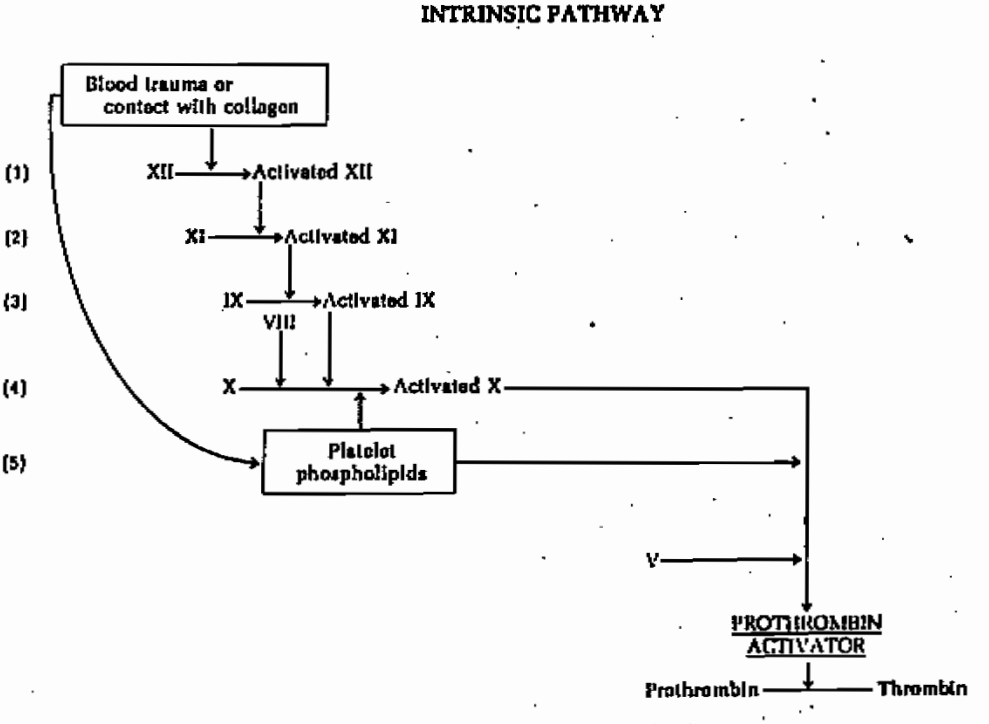

Fig. 2. The intrinsic pathway for initiating blood clotting.

The total coagualtion scheme can be summarized by the following schematized seven formulas:

[1] Injury + platelets $\xrightarrow[\text{aggregation}]{\text{adhesion}}$ PF3+ADP

[2] Tissue thromboplastin+VII $\xrightarrow{Ca^{++}}$ extrinsic activator

[3] XII + XI + PF3 + VIII $\xrightarrow{Ca^{++}}$ intrinsic activator

[4] X + V + PF3 +Ca^{++} $\xrightarrow[\text{intrensic activator}]{\text{extrinsic activator}}$ common activator

[5] Prothrombin $\xrightarrow[Ca^{++}]{\text{common activator}}$ thrombin

[6] Fibrinogen $\xrightarrow{\text{thrombin}}$ fibrin polymer.

[7] Fibrin polymer + XIII $\xrightarrow{Ca^{++}}$ stabilized fibrin.

The basic feature of the coagulation is the conversion of circulating fibrinogen into a stabilized fibrin clot. This occures in two steps: first, fibrinogen is enzymatically converted to fibrin monomer by the action of thrombin and the fibrin monomeric units polymerize. Second, the resulting clot is strengthened and further rendered insoluble by the action of factor XIII.

In order for fibrinogen to be converted to fibrin, thrombin must be generated from its precursor prothrombin.

This reaction is catalyzed by a complex, common activator that consists of the activated form of factor X. factor V, calcium, and PF3. The production of the common activator can occur as a result of two different pathways, the intrinsic and the extrinsic (Fig.1 and Fig.2).

The intrinsic is so named because all its components are present in the circulating plasma. This pathway is probably triggered by both endothelial damage and PF3. The extrinsic pathway is so named because it is triggered by tissue thromboplastin. Considering the firbrinolytic system, fibrinolysis is the major physiological means by which fibrin is disposed of after its hemostatic function has been fulfilled. The mechnism of fibrinolysis is summarised by the followqing formulas:

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                activator
Plasminogen ---------------> plasmin
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fibrin
fibrinogen        plasmin
compiment      ---------------> degredation products
factor VIII
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Plasminogen is a B-globulin with a molecular weight (MW) of 81,000 Daltons. It circulates in plasma in concentration of 10:20 mg/dl. It is activated by a heterogenous group of substances termed "plasminogen activators". Activators reside within the lysozyme of most cells. (Urokinase and streptokinase are examples of specifically identified activators). The activated form of plasminogen, plasmin, is

a proteolytic enzeme with a rather wide spectrum of activities. It cleaves arginyl-lysine bonds in a large variety of substrates, including fibrinogen, fibrin, factor VIII and components of complement. It has a short life in plasma, owing to its inactivation by humoral antiplasmins. Thrombin inhibitors are the varity of substances that act as antithrombins (AT) and inhibit other processes which develop in the coagulation system. Several of the factors represent non specific effects such as the adsorption of thrombin by fibrin (AT1), the effect of various proteins as prothrombin derivatives (ATIV). Abnormal proteins (dysprotenemia) (ATV) and fibrin degradation products (ATVI). (ATII) is Heparin cofactor and it is identical to (ATIII) produced by the liver. It is a progressive inhibitor and neutralizes large quantities of thrombin slowly over a period of minutes to hours when acting alone. In contrast, when ATIII is altered by the attachment of Heparin, neutralization of thrombin is instantanous. Antithrombin III (with Heparin or without it) also effectively neutralizes other activated proteases including factors X,IX, and XII. Deficiencies of AT III in liver disease and as a familial disorders can lead to an increased incidence of thrombo-embolic disease (Russell et.al. 1979).

A century ago Virchows described the basis for much of our present understanding of the gensis of venous thrombosis. In 1860 he postulated a triad of factors which predisposed to thrombosis:

1- changes in blood coagulability;

2- impaired blood flow resulting in venous stasis, and

3- alteration or damage to the intima of the vein (Virchow 1860).

Certain physiological changes of pregnancy predispose to thrombosis as pregnancy increases coagulation of blood and causes venous stasis.

Effects of Pregnancy on the Coagulation Factors:

Pregnancy exerts profound effects on the coagulation mechanism. The so called hypercoagulation state evidenced by the antepartum increase in plasma factors prepares the parturient for placental separation.

Some investigators have described a moderate decrease in the number of platelets per unit volume which slowly progresses as pregnancy advanced with further decrease after delivery to increase again markedly by the 3rd to 5th postpartum days; with no change in adhesiveness (Pitkin and Witte 1980). Others found that there is no remarkable change in their number, appearence or function (Williams 1980). Fibrinogen markedly increases during antepartum period; no change during labor but promptly decreases after placental delivery and increases again back to predelivery level by the 3rd to 5th day with slow decrease thereafter (Russel et.al 1979).

Plasma fibrinogen measured as thrombin-clottable protein in normal non-pregnant women average very close to 300mg/dl. During normal pregnancy, the concentration of fibrinogen increases about 50%, averaging about 450mg late in pregnancy, with a range from approximately 300 to 600 mg.dl which contirbutes greatly to the striking increase in the blood sedimentation rate (Williams 1980). Prothrombin shows no change. Factor V increases immediately after pacental delivery, slowly returns to normal by day 7. factors VII, IX and X progressively increase during pregnancy; with gradual decrease in puerperium. Factor VIII progressively increase during pregnancy; then decreases after delivery with secondary increase and then gradual decrease (Russell 1979). Factors XI and XIII decrease during pregnancy with gradual increase back to normal level in puerperium (Copland 1969). Fibrin split products increase in labor and immediately postpartum (Bonnar 1969). Fibrinolysis decreases after the 1st trimester with prompt increase back to normal after delivery (Margulis et.al. 1954). These changes are summarized in table 1.

High molecular weight soluble fibrin-fibrinogen comlexes circulate in normal pregnancy and lower levels of antithrombin III and increased capacity of neutralizing Heparin have been equated with a continuing low grade process of intravascular coagulation with fibrin deposited in the intervillous space of the placenta and in the walls of the spiral arteris that supply blood to the intervellous space (Bonnar 1978).