COMPARATIVE STUDIES OF BLOOD COAGULATION IN PATIENTS WITH ECLAMPSIA, LATE PREGNANT AND NON-PREGNANT WOMEN

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An increased incidence of thromboembolism has been associated with the post-operative period[2], pregnancy[17], post partum state[22], myocardial infarction[14], ulcerative colitis[10], and malignant diseases, particularly cancer of the pancreas[15], Increased platelet stickiness[31], rises of the levels of coagulation factors[16, 17], and a decrease in heparin cofactors[24] have been suggested as reasons for thromboembolism in these conditions. In patients with cancer, increase in individual or several clotting factors[1, 16, 27] and an increase in urokinase inhibitor[23] have been observed. The short prothrombin time of late pregnancy has long been known, and can be accounted for by an increase in factors VII and X.[17]

This study evaluates the frequency and degree of changes in selected coagulation factors and their predicative value as well as specificity of such changes for impending thrombosis or consumption coagulopathy in patients with eclampsia as compare to late-pregnant and non-pregnant women. The pregnant state was also studied because it constitutes a common temporary and reversible physiologic condition that is frequently complicated by thromboembolism. Moreover, clotting abnormalities with hemorrhagic phenomena, reflecting the other side of the coin, are also frequent in pregnancy. The most important reason is to compare these changes and the findings in eclampsia.

Materials and method

Blood samples from twelve patients with eclampsia which constituted the first subject group were studied on the day of admission or 1-2 days after hospitalization in Obstetrical Department Chulalongkorn Hospital, Chulalongkorn University. None of these patients were receiving any treatment within one month prior to admission. Patients receiving estrogens, androgens, or progestrogens were not included in the study.

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The second group consisted of 20 normal female medical students of Chulalongkorn University. This control group was comparable in age with eclamptic patients. These controls were also not recieving any medication prior and during this study.

The third group consisted of 20 normal late-pregnant women, taken from the obstetric clinic of Chulalongkorn Hospital during the last trimester of pregnancy (about 36 – 38 weeks of gestation). Patients receiving estrogens, androgens or progestrogens were again, not included in the study.

Blood samples were obtained after an overnight fast. They were collected in 1 : 9 volume by volume of 3.8 % sodium citrate in a polycarbonate tube. Blood was drawn in a syringe after a clean venepuncture. All determinations were performed on fresh plasma. The prothrombin time was determined by the method of Quick[21], using a commercial thromboplastin (Difco Laboratories, Detroit, Mich.); the activated partial thromboplastin time was determined by the method of Hardisty and Ingram[7], using a commercial phospholipid (Platelin, Warner Chilcott Laboratories, Morris Plains, N.J.) and the fibrinogen assay by the method of Fowell.[9]. The thrombin time and one-stage factor VIII assay were done by the method of Hardisty and Ingram[7], Substrate plasma from a single hemophiliac subject was used for all tests of factor VIII activity. The one-stage factor V assay was done by the mtehod of Biggs and Mac Farlane[3]. The platelet adhesiveness was done by using glass beeds "superbrite" type from Minnesota Mining. The plasma recalcification time was performed by the method of John B. Miale[9].

Results

Prothrombin time

The mean value of the prothrombin time for normal subjects was 12.25 seconds (Fig. I) In the late pregnant group the mean prothrombin time was 12.03 seconds. In the eclampsia group the mean prothrombin time was 10.75 seconds. Thus, both the normal late pregnant group and eclampsia group had short mean prothrombin time when compared with normal non-pregnant subjects. Of the 7 patients with eclampsia who had shortened prothrombin time, 5 had an elevated factor II, 7 had elevated factor VII and 6 had elevated foctor V. The mean prothrombin time in the eclampsia group was shorter than in the late pregnant group.

Partial thromboplastin time

The mean partial thromboplastin time for normal subjects was 82.5 seconds (fig. II). In the late pregnant group the mean partial thromboplastin time was 61.75 seconds. In the eclampsia group the mean partial thromboplastin time was 43.25 seconds.

The partial thromboplastin time was accelerated in both late pregnant and eclmpsia group. In comparison with normal subjects the acceleration was more significantly high in eclampsia patients than in late pregnaney. Of the 10 prtients with eclampsia who had a shortened partial thromboplastin time, 8 had an elevated factor VII and 5 had elevated factor V levels,

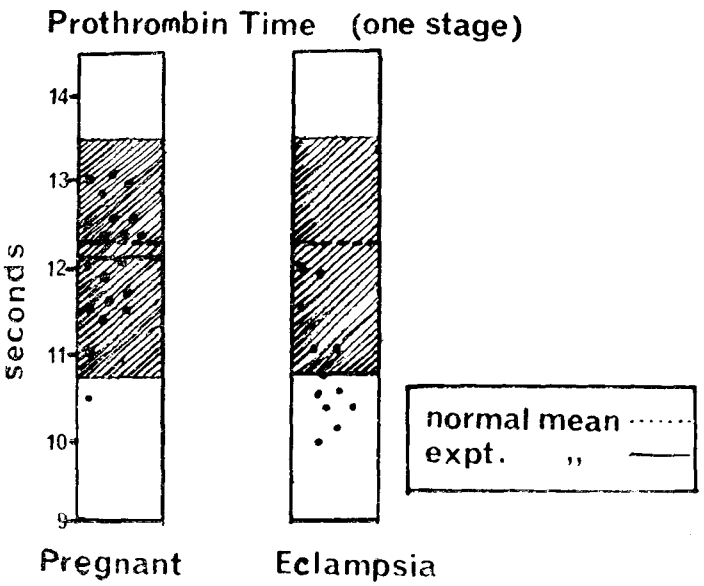

Figure I: The one stage Prothrombin time in patient with eclampsia and late pregnancy.

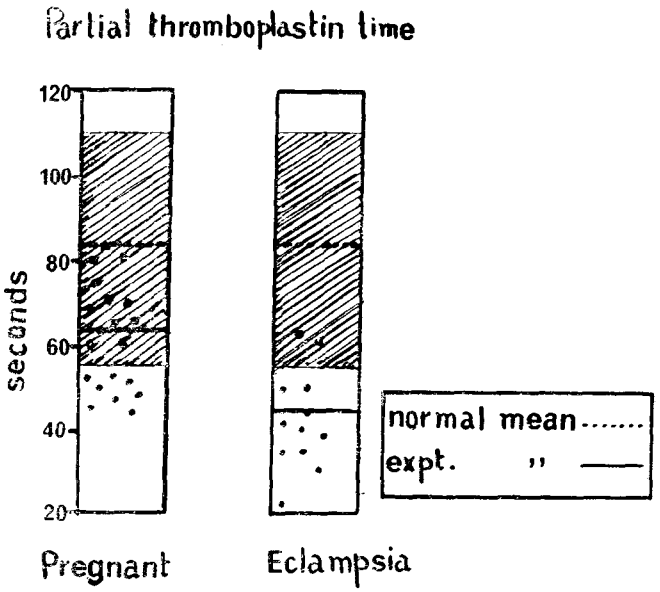

Figure II: The partial thromboplastin time in patients with eclampsia and normal late pregnancy.

Factor V

An increase of factor V was noted in 58.3% of patient with eclampsia and 20% of normal late pregnant patients. The mean value of factor V in eclampsia group was 133.6% (Fig. III) which was significantly higher than normal subjects (mean value was 105. 3%). The mean value of eclampsia patients was higher than that the late pregnant group (mean value was 107.7%).

Factor II

An increase of factor II was noted in 5 cases from 12 eclampsia patients (41.66%). In patient with late pregnancy, none showed an elevated level of factor II (Fig. IV). The mean value of factor II in eclampsia patient was 125.5%, in normal subjects was 105.05% and in the late pregnant group was 105.9%.

Factor VII

The mean factor VII level in eclampsis patients was 131.16% which was significantly increased when compare to normal subjects that was only 89.45% (Fig. V). The mean factor VII level in the late pregnant group was 107.35% which was only a little nigher than normal mean. The factor VII value was higher than the upper limit of normal in 75% of eclampsia and none in late pregnant group.

Factor VIII

The mean factor VIII leval was 82.2% in normal subjects, 92.25% in late pregnancy and 124.33% in eclampsia group (Fig.VI). The mean factor VIII level was significantly high in eclampsia and late pregnant patients. The factor VIII level was higher than the upper limit of normal in four eclampsia patients and one of the late pregnancy. However the mean factor VIII level in the later group was not significantly high as much as in eclampsia group when compare with normal subjects. One patient with eclampsia had level of factor VIII in excess of 300%. The highest concentration of 310% was observed in 21 year old patient who had almost continuous convulsion, blood pressure of 240/120 mmHg. and heavy albuminuria. All the abnormal coagulogram turned to be normal in one week after delivery. She had no clinical evidences of thrombophlebitis or thromboembolim.

Fibrinogen

The mean value of fibrinogen in normal subjects was 218.06 mg% (Fig. VII) The mean fibrinogen in eclampsia patients was 513.75 mg% and in late pregnancy was 465.25 mg%. There was an increase in fibrinogen level in 11 of 12 of eclampsia group and 19 from 20 in late pregnant group. The mean increase of both groups was significantly high when compared with normal subjects, but the increased fibrinogen level of eclampsia was higher than the late pregnancy. None of eclampsia and late pregnant groups had demonstrated a decrease in fibrinogen level.

Thrombin time

The thrombin time was shortened (1–3 seconds) in 6 patients with eclampsia (50.0%) and 10 patients with late pregnancy (50.0%). None of them had prolonged thrombin time.

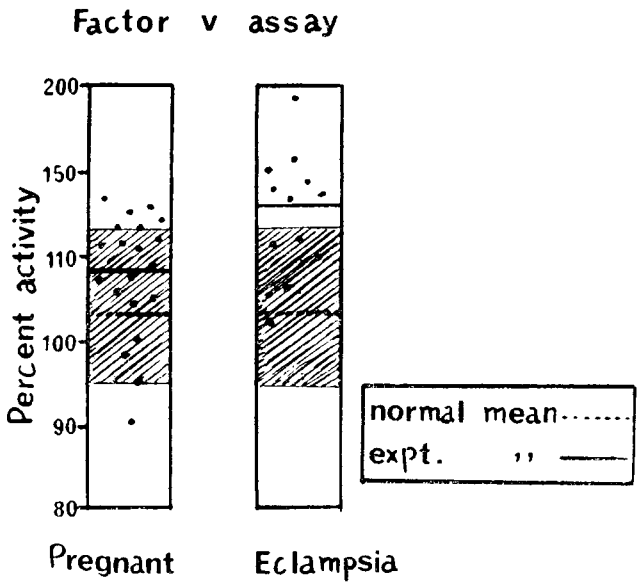

Figure III : Factor V activity in patients with eclampsia and late pregnancy.

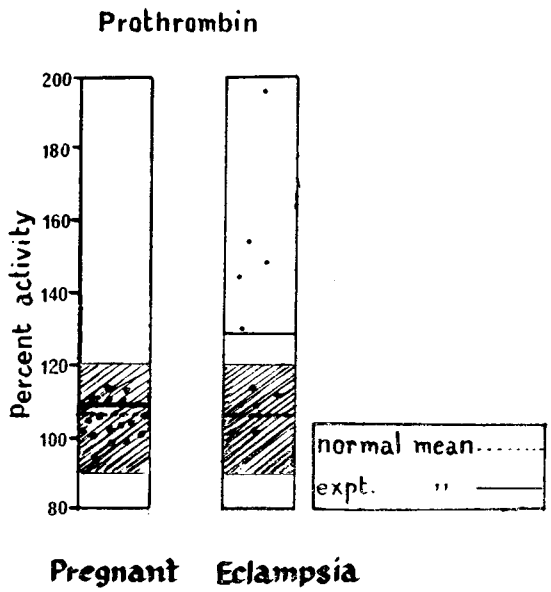

Figure IV : Activity of factor II in patients with eclampsia and late pregnancy.

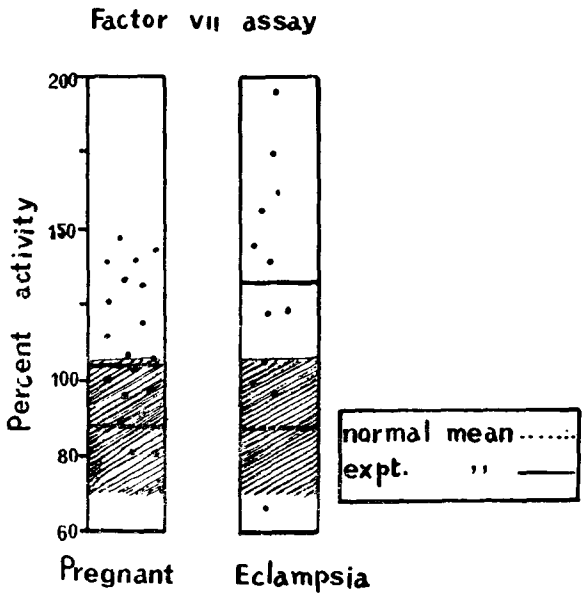

Figure V : Activity of factor VII in patients with eclampsia and late pregnancy.

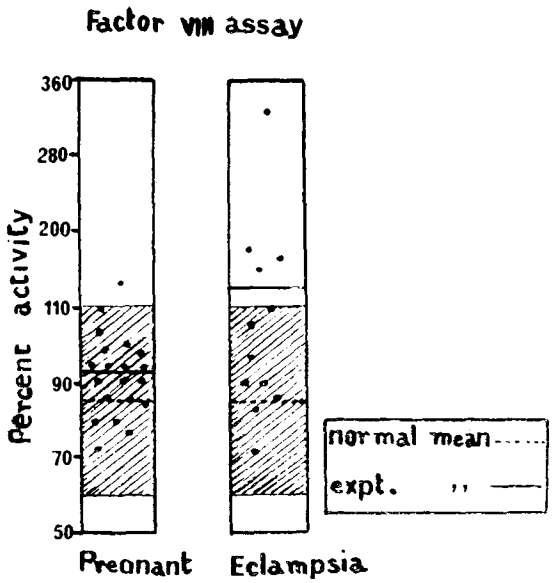

Figure VI : Activity of factor VIII in patients with eclampsia and late pregnancy.

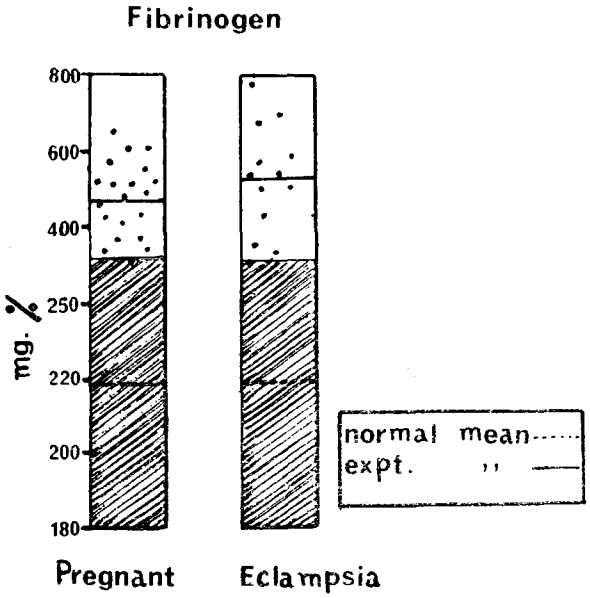

Figure VII : Concentration of plasma fibrinogen in patients with eclampsia and late pregnancy.

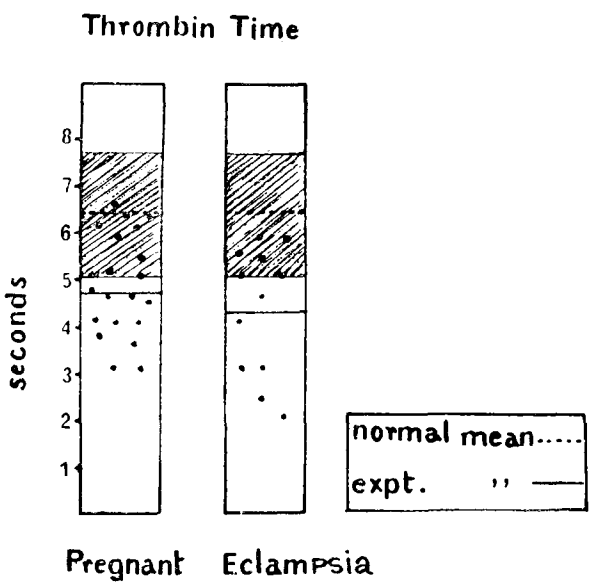

Figure VIII : The thrombin time in patients with eclampsia and late pregnancy.

Platelet count

The mean platelet count of normal subjects was 393,000 per mm^3, eclampsia group was 735,066 per mm^3 and in the late pregnant group was 514,850 per $mm.^3$ (Fig. IX). The mean platelet count was increased in patients with eclampsia, but not in the group of late pregnancy which is slightly higher than normal mean but still within normal range.

Platelet adhesiveness

The mean percentage of platelet adhesiveness in the normal subjects was 51.85%, in eclampsia group was 77.61 % and in late pregnant group was 64.15% (Fig X). The means of the later two were significantly different from the mean of normal subjects. There was increased platelet adhesiveness in 11 cases (91.7 %) in eclampsia group, but only 11 cases (55%) in late pregnant group. The percentage of platelet adhesiveness in eclampsia group was higher than late pregnant group.

Recalcification time

The mean recalcifacation time in normal subjects was 170.45 seconds, in eclampsia patients was 165.83 seconds and in the late pregnant group was 170.5 seconds (Fig. XI). There was no significantly different mean. Neither the eclampsia nor normal pregnant group was asssociated with shortening of the mean recalcification time.

Statistical Interdependence of Data

The interrelation of certain tests were evaluated by regression analysis. There was a significant correlation between the prothrombin time, factor V and factor VII levels in patients with eclampsia. Shorter prothrombin times were associated with an increase in factor V and VII and vice versa, but no significant correlation was observed in late pregnant group. In the later group alterations of factor II and factor X apparently were present that

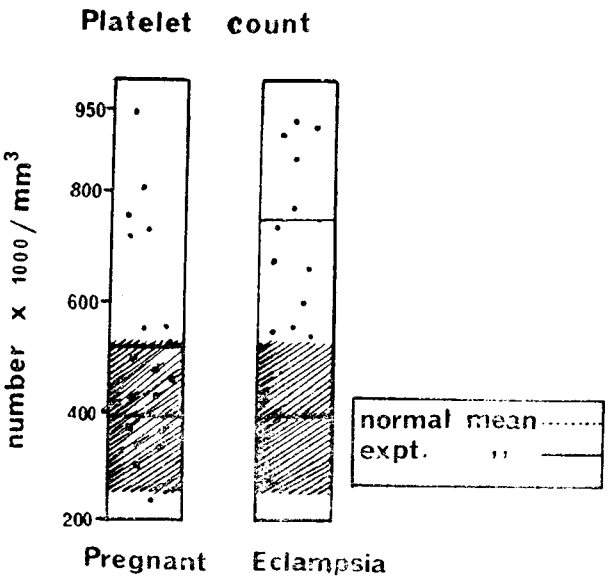

Figure IX : Value of the platelet count in patients with eclampsia and late pregnancy.

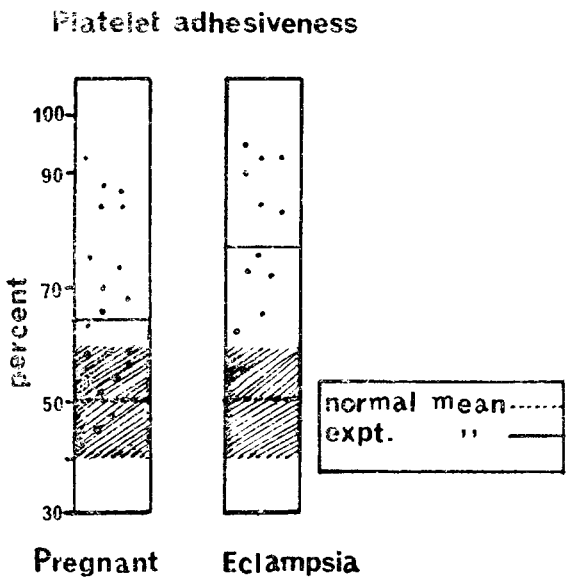

Figure X : Percentage of platelet adhesiveness in patients with eclampsia and late pregnancy.

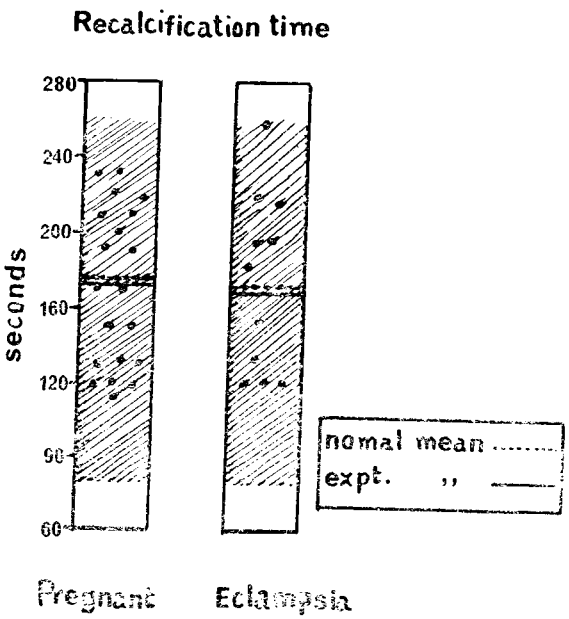

Figure XI : The recalcifacation time in patients with eclampsia and late pregnancy.

minimized the effects of changes in factor V and VII in altering the prothrombin time. No correlation was observed between the level of factor VIII aad the prothrombin time in any of the three groups of patient. There was asignificant correlation between the level of factor VIII in eclampsia group, with shorter values of partial thromboplastin time associated with higher leval of factor VIII. Although the shorter values of partial thromboplastin time were associated with higher level of factor V in eclampsia group. No such correlation in late pregnant group In patients with eclampsia the prothrombin time tended to be shorter with shorter partial thromboplastin times. There was no correlation between the prothrombin time and the partial thromboplastin time in the control and late pregnant groups.

Discussion

Some hematological paramaters normally assume different values in pregnancy from those obtaining in the non-pregnant states. The previous studies demonstrated changes in coagulation tests in bleeding disorders.

The present investigation demonstrated significant changes levels of clotting factors in patients with eclampsia and has extended these observations to include patients in pregnancy. It became apparent as the work paogressed that the later group of patients had similar abnormalities in coagulation tests. Thus, similar alterations were observed in the prothrombin time, partial thromboplastin time, factor V, VIII, fibrinogen, thrombin time, platelet count and platelet adhesiveness. Two distinct differences in patients with eclampsia and late pregnant groups were noted. First, the mean platelet count in eclampsia group were significantly higher than in the late pregnant group. Secondly, percentages of platelet adhesion test were much higher in eclampsia group than in late pregnant group.

The level of factor VIII and V were increased in 33.3 % and 58.3 % respectively of patients with eclampsia, increases of factor VIII greater than 300 % were found in one case of eclampsia patients and none in the late pregnant patients.

Fibrinogen levels are elevated in a wide variety of conditions, including cancer[16], pneumonitis[5], myocardial infarction[12], multiple sclerosis[19], rheumatoid arthritis[20], rheumatic fever[11] and arterial occlusion[8]. Tissue injury is believed to be common to each of these entities. It is not surprising that substantial increases in fibrinogen were observed, both in eclampsia group and the late pregnant group in this study. The highest mean value was observed in patients with eclampsia, but the mean fibrinogen concentration was elevated in both groups.

Thrombotic complications in patients with pregnancy have been recognized for a long time[17]. Thus a hypercoagulable state has been postulated to exit with thrombosis in pregnancy and can be produced in experimental animals[4,28]. Wessler and Thye Yin[29] have shown recently that systemic hypercoagulability in animals was not related to the absolute rise in the level of a specific factor but to the presence of activated forms of clotting factors. Activated forms of clotting factors, hower, are rapidly removed from the circulation by the liver[25] and by plasma[30]. Thus, their transient presence in the blood of patients with pregnancy might be difficult to detect. Increases of nonactivated clotting factors are easily detected and the relation, if any, between elevated levels of coltting

factors in pregnancy and intravascular coagulation or thrombosis is of interest.

The rise in the level of various factors has been attributed to their compensatory overproduction as a result of low-grade intravascular coagulation[16]. The occurenc of the higher levels of clotting factors may well predispose to more massive thrombosis once coagulation is initiated[13].

There was a significant association between shorter prothrombin times and partial thromboplastin time values in both groups of late pregnancy and eclampsia, only difference was the times in eclampsia group were much shorter than in the late pregnant group. This correlation could have resulted from a circulating thromboplastic material, or multiple elevations of clotting factors or both. The mean levels of factor VIII and factor V were greater in eclampsia patients. The level of an individual factor resulted from the balance of of production, utilization or destruction or all of these. The late pregnant group may have had higher rates of production of clotting factors, but the rate of destruction may also have been higher in this group, that is why they have the high level of clotting factors less than the eclampsia group. Other coagulation factors, not measured in this study, may also have been altered to affect the partial thromboplastin time.

None of our patients with abnormalities of coagulation tests or platelet adhesiveness had detectable thrombophlebitis or clinical intravascular coagulation.

More than a century ago Virchow[26] postulated three etiologic factors in thrombotic disease: blood hypercoagulability, blood stasis and vascular injury. There is now no question that the last two of the triad are extremely important, but there is still considerable controversy regarding increased blood coagability as a significant pathogenetic factor. This thromboembolic phenomenon may begin spontaneously, or may be triggered either by the release into the circulation of thromboplastic tissue elements from the gravid uterus or its confines[5,9] or by increased venous stasis or endothelial vascular damage. The presence of several clotting factors and platelet adhesiveness abnormalities may have value in predicting impending intravascular coagulation and may justify the instution of anticoagulant therapy.

Summary and conclusions

Earlier studies demonstrating increased factorVII, X activity during the last trimester of pregnancy have been confirmed and extended. The present investigation shows that the factors V, VII, VIII are frequently elevated, even much more frequently and in higher level in eclampsia.

The abnormally higher levels of some factors do not reflect "activated" material in the circulation but, more probably, increased levels of the relatively inert precursors, which, as in normal serum, can be profoundly activated by thromboplastin.

The increases in these clotting constituents and other recognized changes in fibrinogen, platelet count and platelet adhesiveness constitute a truly hypercoagulable state, together with known circulatory stasis in the pregnant women, present a vulnerable basis for thromboembolic complications, or may have value for predicting intravascular coagulation in patients with pregnancy especially eclampsia because of these abnormal changes.

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