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PLASMA FIBRINOGEN AND FIBRINOLYTIC ACTIVITY IN NORMAL AND ABNORMAL PREGNANCY

by

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Introduction

Haemorrhage during pregnancy and labour remains one of the major causes of death despite advances in antenatal management, anaesthesia and availability of blood transfusions. That faulty coagulation of blood can be a cause of haemorrhage was suggested by De Lee in 1901. Dieckman in 1936, demonstrated for the first time the nature of clotting defect. Moloney *et al*, included fibrinogen as an adjuvant to blood transfusion in the treatment of this condition. Later, similar defects were reported to occur in association with retention of a dead foetus in utero and amniotic fluid embolism.

More recently the presence of fibrinolytic activity has been shown to be increased during pregnancy when the pregnancy is associated with pathological conditions like eclampsia, toxaemia of pregnancy, septic abortion, intrauterine death of foetus, etc. Although the role of fibrinolytic activity in causing haemorrhage was first suspected by Moloney *et al* (1949), the levels of its activity in different periods of gestation were not reported until 1968 when Biezenski and Moore reported the gradual decrease in its activity during pregnancy and labour, and the sudden rise in puerperium. The mechanism of this reduced activity is still not fully understood. Gillman and Naidoo (1959) opine that the endocrine changes in pregnancy are responsible for this change in fibrinolytic activity. Since very few reports on haemorrhage due to increased fibrinolytic activity have been reported from India, the following prospective study was undertaken at the Department of Obstetrics and Gynaecology of the B. J. Medical College and Sassoon General Hospitals, Poona.

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Material and Methods

Two groups of patients were selected for study. Group I consisted of 80 patients who were considered normal and served as controls. These patients were selected from antenatal clinic, gynaecological clinic, labour wards and postnatal wards.

Group II consisted of 61 patients with the following obstetric complications: Accidental haemorrhage, toxaemia of pregnancy, septic abortion, intra-uterine death syndrome, vesicular mole, eclampsia and postpartum haemorrhage.

Method

Ten ml. of blood was collected from the antecubital vein of each patient, in bulbs containing 3.4% sodium citrate. It was either used immediately for estimations or stored at 4°C until so used.

Plasma fibrinogen levels were estimated by sodium sulphate fractionation as described by Goodwin; and Fibrinolytic activity was estimated by the method of Dilute Clot lysis time described by Fearnley. The percentage of lysis of clot was calculated by the formula described by Dass and Sircar (1968).

Results

Table 1 shows patients comprising Group I and Group II and their respective parity. In Group I there were 10 patients in each of the first, second and third trimesters of pregnancy. Ten patients in well established labour, 10 each on the 4th and 7th days postpartum and 20 patients with normal biphasic menstrual cycles.

Group II comprised of 11 patients with abruptio placentae, 2 with intra-uterine death of foetus, 9 with septic abortion, 17 having toxaemia of pregnancy, 3 having eclampsia, 5 with molar pregnancy and 4 having postpartum haemorrhage.

All the 11 patients with abruptio placentae were in third trimester of pregnancy and presented with antepartum vaginal bleeding during labour. Five of these 11 patients showed coagulation defects, had severe postpartum haemor-

TABLE 1
Patients Grouped According to Parity

Group—I	Primipara	II para	Multipara
Non pregnant 20	–	–	–
Patients in 1st trimester	5	3	2
Patients in 2nd trimester	4	4	2
Patients in 3rd trimester	3	2	5
Patients in Labour	2	3	5
Puerperium on 4th day	1	3	6
Puerperium on 7th day	4	0	6
Group—II			
Premature separation of placenta	0	4	7
Intrauterine death syndrome	2	4	3
Septic abortion	0	4	5
Toxaemia of pregnancy	12	5	0
Eclampsia	3	–	–
Molar pregnancy	1	2	2
Post partum Haemorrhage	1	2	1

rhage and required one or more blood transfusions.

Seventeen patients had mild to moderate toxaemia of pregnancy. All had 2 or more signs of toxaemia. Twelve were primiparae and 5 were second para.

All the 3 patients who had eclampsia were primiparae, with B.P. above 160/100 mm of Hg., massive oedema and proteinuria.

Five patients had vesicular mole. Two of them presented with bleeding per vaginam and aborted soon after admission. The other 3 had associated toxaemia of pregnancy.

In none of the 4 patients with postpartum haemorrhage was there any evidence of either trauma or retained products (Table I).

Plasma Fibrinogen Levels and Fibrinolytic Activity

Table II shows the plasma fibrinogen levels and fibrinolytic activity in normal patients. The mean plasma fibrinogen level in non-pregnant patients was 253 mgm%. The level increased gradually, rising to a mean of 383 mgm% in the third trimester, further rose to 425 mgm% during labour and dropped immediately thereafter to reach near non-pregnant levels of 218 mgm% on 7th day postpartum.

The lytic activity was 74% in non-pregnant patients and gradually reduced from 77% in the first trimester to 57.7% in the second trimester and to 50% in the third trimester. There was a further fall to 40% during labour. Soon after labour it rose to 63% on the 4th day and reached non-pregnant levels of 77% on the 7th day postpartum.

Thus, plasma fibrinogen levels and fibrinolytic activity were inversely proportional to one another.

Table III shows fibrinogen level and fibrinolytic activity in patients with obstetric complications.

(a) The mean plasma fibrinogen level in 11 patients with accidental haemorrhage was 185 mgm%. All showed a definite hypofibrinogenaemia.

(b) In the 11 patients with intra-uterine foetal death, the mean plasma fibrinogen level was 299 mgm% with an average plasma fibrinolytic activity of 68%. Both these showed wide range of activity.

(c) The mean plasma fibrinogen levels and fibrinolytic activities in patients with septic abortion were 209 mgm% and 90.9%. The increased fibrinolytic activity

TABLE II

Mean Plasma Fibrinogen Levels and Fibrinolytic Activity in Non-pregnant, During Pregnancy, Labour and Puerperium

Group	Plasma fibrinogen in mg%		Fibrinolytic activity index in %
	Mean	Range	
Non pregnant (20)	253	220–360	74%
Pregnant 1st trimester 14 weeks	279	240–310	77%
Pregnant 2nd trimester 24 weeks	351.8	300–460	57.7%
Pregnant 3rd trimester 36 weeks	382	300–480	50.0%
During labour	425	360–490	40.0%
Puerperium 4th day	218	280–320	63.0%
Puerperium 7th day	301	190–250	77.6%

TABLE III
Plasma Fibrinogen Levels and Fibrinolytic Index in Obstetrical Complications

Group II		Plasma fibrinogen in mg%		Fibrinolytic index in %
		Mean	Range	
Abruptio placentae	(11)	185	92–280	94%
Intrauterine death syndrome	(12)	299	160–420	68%
Septic abortions	(9)	204.4	180–280	90.9%
Toxaemia of pregnancy	(17)	282.35	190–360	68.4%
Eclampsia	(3)	206.7	180–260	93.3%
Vesicular Mole	(5)	350	240–440	44.0%
Post-partum haemorrhage	(4)	200	180–240	90.0%

was seen to fall when patients were treated with antibiotics and blood transfusions.

(d) The mean fibrinogen level in patients with toxaemia of pregnancy was 340 mgm% with a fibrinolytic activity of 68.4%.

(e) In patients with eclampsia the mean plasma fibrinogen level was 206.7 mgm% with a fibrinolytic activity of 93.3% in labour.

(f) The 2 patients of vesicular mole who aborted had plasma fibrinogen levels of 390 and 340 mgm% with corresponding fibrinolytic activities of 60% each. The 3 who presented with toxaemia had an average plasma fibrinogen level of 340 mgm% with an average lytic activity of 40% The average fibrinogen level of all 5 patients was 350 mgm% and lytic activity was 44%.

(g) The mean plasma fibrinogen level of the 4 patients with postpartum haemorrhage was 200 mgm% and lytic activity was 90%.

Increase of clotting factors and reduced lytic activity are a defence mechanism against excessive loss of blood during parturition and are useful for rapid and effective haemostasis. The mechanism whereby these alterations are produced are ill-understood. However, that fibrinogen levels gradually increase in parallel with the period of gestation is well established and our results compare favourably with those of other investigators.

In the earlier studies on fibrinolytic activity, conflicting results were reported. Fearnley *et al* (1957) demonstrated this to be due to the faulty technique of preservation of plasma at room temperature which destroyed the fibrinolytic activity. Storage at 4°C gave uniform results. It was in 1958 that Biezenski and Moore reported gradual decrease in fibrinolysis during pregnancy and labour, and rapid increase in early puerperium. Similar resullts have been reported by Sharper *et al* (1968) and Apte *et al* (1968). The present series also shows a similar trend.

Abruptio placentae is the most widely studied complication of pregnancy and labour since it gives rise to serious coagulation failure. Although hypofibrinogenaemia was found in all our patients, only 46% had clinical features of coagulation failure. Bourne and Reidel report 5%, Coopland *et al* (1968) report 20% and Pritchard and Breeken (1967) report 38% of their patients as having coagulation failure. Hibbard and Jeffcoate (1966) state that 73% patients with hypofibrinogenaemia do not suffer from postpartum haemorrhage and the only indication for treatment is active haemorrhage.

In patients with intra-uterine death of foetus, the mechanism of fibrinogen depletion is controversial. It is recognised nevertheless that the greater the gestational age before death and the longer the duration of retention of dead foetus, the greater is the chance of hypofibrinogenaemia. The derangement therefore rarely develops because majority of foetuses are expelled within a few weeks following their death and only 5% of foetuses remain in utero after 4 weeks. All our patients aborted by the end of the first week and none developed coagulation failure despite low fibrinogen levels. Similar values are reported by Dass and Sircar (1968). In 21 patients with foetal death in utero, Pricohard (1955) reported a linear fall in fibrinogen levels beginning 3 weeks after foetal death. Of the 8 patients who developed hypofibrinogenaemia only 3 had haemorrhagic manifestations.

Mckay and Corey (1964) studied fibrinogen level and fibrinolytic activity in 21 cases of septic abortion. In 11 treated and 10 untreated cases the levels were not very different from normal. In the present series all patients showed hypofibrinogenaemia and high fibrinolytic activity.

In 17 patients with toxaemia, the plasma fibrinogen levels were lower than in normal patients and fibrinolytic activities were raised above normal for the same periods of gestation. This is corroborated by the findings of the Birmingham eclampsia study group (1972). However, Dass and Sircar (1968) and Bonnar (1969) have found no significant differences from normal pregnant women. Similarly, Bonnar (1971) has reported very minor changes in fibrinogen levels in 2 of his patients with eclampsia.

The mean plasma fibrinogen levels and fibrinolytic activities in the present series of patients with vesicular mole compare well with those reported by Dass and Sircar (1968). However, very little work is reported on molar pregnancies.

In all the 4 patients who had postpartum haemorrhage there were low plasma fibrinogen levels and high fibrinolytic activity. Since no obvious cause for the haemorrhage could be detected the high lytic activity must be the only reason for bleeding.

Summary

1. Twenty non-pregnant patients with biphasic menstruation and 10 each in the first, the second and the third trimesters of pregnancy, in labour, 4th day of puerperium and 7th day of puerperium were studied.

2. Sixty patients with complications of pregnancy like abruptio placentae, septic abortion, toxaemia of pregnancy, eclampsia, molar pregnancy and postpartum haemorrhage were studied.

3. The patients in the 3 trimesters of pregnancy, labour, puerperium, 4th and 7th day, had their plasma fibrinogen levels and fibrinolytic activity indices compared.

4. Plasma fibrinolytic activity and fibrinolytic indices in complications of pregnancy were compared.

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