A STUDY OF BLOOD COAGULATION COMPONENTS DURING PREGNANCY

By

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Whole blood and plasma calcium clotting times, prothrombin, fibrinogen level and the fibrinolytic activity of the blood in normal healthy women and in ladies during third trimester of pregnancy have been estimated. No significant change of the whole blood clotting time but an appreciable decrease of calcium clotting time was observed. One stage prothrombin time in pregnancy was seen to be double that of normal state while the two stage time did not exhibit any significant increase. Fibrinogenaemia is a regular feature of pregnancy. The normal values of 200 mg% are found to be enhanced to 275 mg%. Fibrinolytic activity is considerably decreased during pregnancy.

The need for keeping a flow sheet of coagulation components for use in obstetrics practice is implied. The degree of coagulation defects should be kept constantly in mind, particularly deficiency in fibrinogen and manifestations of fibrinolytic activity.

Many morphological, physiological and biochemical changes are known to occur during pregnancy. During the pregnancy the mother is susceptible to certain vascular lesions, chief among them being, the tendency for 'Intravascular thrombus' formation. During parturition, acute haemorrhage and fatal bleeding may take place. An appreciation of the factor that these thrombotic and haemorrhagic phenomenon are not merely due to the involvement of the lesions in the vascular walls or localized abnormalities of the uterus or vagina but possibly to inherent alterations in the coagulation mechanisms, has changed the therapeutic approach to such disorders.

It is essential to know the range of variations of the coagulation factors during normal pregnancy, if any specific component has to be incriminated as a causative agent for the vascular disorder.

Knowledge of any alterations in the coagulation components during the course of pregnancy is of clinical importance for its prognostic value. This would assist in maintaining a closer watch for any untoward incidents in women exhibiting abnormal variations.

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Investigations have been undertaken to establish the normal ranges of some of the coagulation components in non-pregnant healthy ladies and in women during the latter period of pregnancy.

METHODS

Healthy ladies between the ages of 18 and 35 yrs, belonging to same socio-economic group, having at least one child and the younger one more than $1\frac{1}{2}$ yrs old were selected to obtain the data for the non-pregnant state.

For determination of the pregnancy changes, ladies of the same age and socio-economic group as normals, attending the antenatal clinic of St. Martha's Hospital, Bangalore, were selected. These ladies were generally healthy with no manifestation of anaemia or any other clinical disorders and were in the third trimester of pregnancy.

Collection of blood sample :—All blood samples were collected in the morning between 9 and 11 a.m. six ml of blood were drawn into a dry sterilized syringe from the antecubital vein and collected in sample tubes containing 3.8 per cent sodium citrate in normal saline as an anticoagulant in the proportion of 9 : 1.

The coagulation components were determined as early as possible after the collection of the blood. They were (i) Whole blood clotting time, (ii) Calcium clotting time, (iii) Prothrombin time by one stage method, (iv) Prothrombin time by two stage method, (v) Fibrinogen estimation, and (vi) Fibrinolytic activity.

The methods of preparation of the reagents and the details of the techniques adopted have been described in earlier communications (Chiplunkar and Sirsi, 1962; Chiplunkar *et al* ., 1963).

RESULTS AND DISCUSSION

The values of blood coagulation components for healthy non-pregnant females are shown in Table I. Table II depicts the same for women during the latter half of pregnancy and comparative evaluation is shown in Fig. 1.

The significance and the likely interpretations for the variations of coagulation components in general have been described in detail in an earlier paper (Chiplunkar *et al.*, 1963).

TABLE I

Coagulation components in healthy ladies

Serial No.	Clotting time.				Prothrombin		Fibrinogen	Fibrinolytic activity
	Whole blood Min	Sec	Calcium Min.	Sec.	Stage one Sec	Stage two Sec	mg/100 ml Plasma	Percentage lysis of whole clot
1	6	45	3	37	66	24	232.7	2
2	4	40	3	37	51	15	231.3	4
3	3	50	3	31	50	15	167.3	4
4	5	30	3	38	54	22	152.4	7
5	4	35	3	39	46	20	160.8	8
6	4	35	3	11	51	18.5	195.9	4
7	3	35	2	25	54	16	277.5	6
8	3	50	2	26	59	18	186.4	10
9	3	45	2	48	54	19	242.2	6
10	4	15	3	31	60	21	197.2	6
11	3	0	2	45	70	19	184.9	5
12	5	30	3	35	68	19	216.0	4
13	4	40	3	4	73	19	162.8	10
Mean+ S E —	4	30± 16.4″	3	17± 6.2″	58.2±2.4″	18.9″±0.7″	200.5±10.4	5.85±0.66

TABLE II

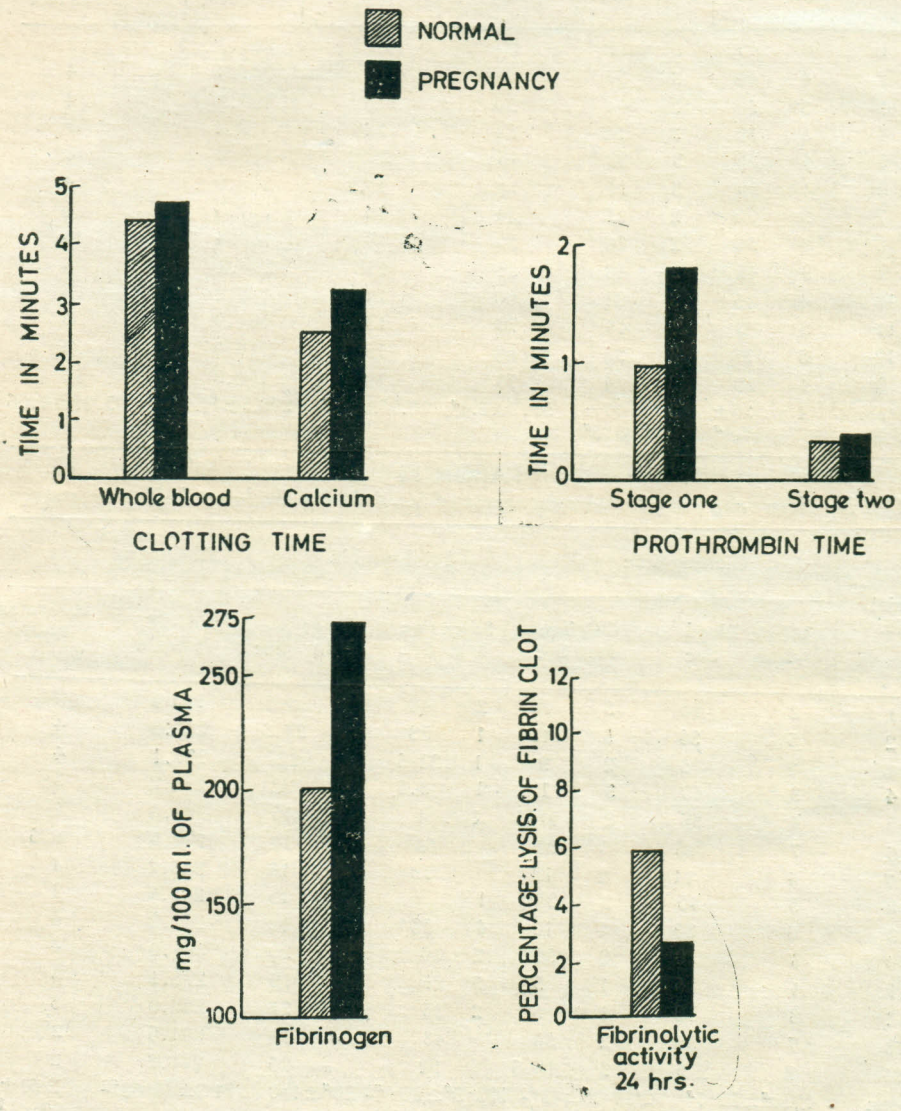
Clotting times and coagulation components of blood during the latter half of pregnancy

Serial No.	Clotting time				Prothrombin				Fibrinogen	
	Whole Blood Min	Sec	Calcium Min	Sec	Stage one Min	Sec	Stage two Min	Sec	mg/100 ml plasma	Percentage lysis of whole clot
1	2	10	3	10	2	40	28		199 6	2
2	5	39	5	15	1	23	23.5		227.6	4
3	2	5	2	9	1	22.5	22		277.1	4
4	3	49	3	1	1	3.5	22		253.2	5
5	4	36	2	31.5	1	1	15		399.3	1
6	7	16	3	52		60	17		272.5	0.5
7	4	14	2	12		59	16		346.2	1
8	5	15	3	22.5	1		15		255.8	1
9	6	35	1	10	4	58	19		272.2	4
10	3	0	0	59	2	20	20		101.9	4
11	4	5	1	5	3	21	18		275.1	3
12	3	10	1	5	2	33	21		282.0	3
13	7	50	2	50		43	19		394.6	2
14	8	5	3	16.5		52	25		261.2	2
Mean S.E.	4′/51″±32·1″		2′34·1″±45″[1]		108·3″±20·5″[2]		20″±1·0		274·3±20·85″[2]	2·61± 0·38[1]

[1] Significant at 5%
[2] ,, at 1%

FIG. 1.

BLOOD COAGULATION COMPONENTS IN NORMAL AND PREGNANCY STATES.



The diminished calcium clotting times observed in pregnancy from the normal 3'14" to 2'34.1" which is statistically significant, may be one of the factors involved in the increased tendency for the thrombus formation during pregnancy.

One stage prothrombin time was found to be significantly high in pregnancy. In contrast, in the two stage method, the prothrombin time of 20" during pregnancy did not significantly differ from normal value of 18·9".

Since the two stage technique is considered to be specific for prothrombin, while other factors come into play in the one stage procedure, our results lead to the conclusion that during the latter half of pregnancy, no appreciable change in the prothrombin concentration of the plasma takes place and the increased prothrombin time seen with the one stage technique is probably due to changes in the other coagulation components like antihaemophic globulin, calcium, factors v, vii and many other factors known to influence the one stage results.

In the method adopted by us for the two stage method, the thromboplastic matter is supplied by the persons erythrocytes themselves and since no alterations are observed by this two stage technique, the thromboplastin component and other factors in the plasma needed for prothrombinase, common for both the methods are not likely to be involved in the prolongation of the time seen in one stage method. Besides, in the one stage, the brain thromboplastin is used which rules out thromboplastin variations as a cause for the prolonged time.

The chief difference in the two methods appears to be in the calcium concentration used. In the one stage, an optimal concentration of calcium is employed while excess calcium is present in the two stage method.

Chemicals through binding of the calcium ions, which are thus lost for the clotting mechanism may interfere with certain calcium dependent coagulation reactive steps. A branched chain polymer of glutamyl peptide in solutions of plasma has been shown to bind calcium and enhance the clotting time (Peters, 1959). Whether pregnancy blood contains similar components which by lessening the availability of calcium prolongs the one stage prothrombin time needs investigation.

Fibrinogen deficiency below 100 mg per cent can cause lengthening of one stage but can also be ruled out as a causative factor since fibrinogen content is elevated during pregnancy. Since prothrombin reduction and fibri-

nogen dimunition can both be eliminated, an increase in the antithrombin content of the plasma, lack of vitamin K and deficiency of the factors v and vii have to be considered.

While the trend of the rise in fibrinogen level was similar to that observed amongst American women, the actual values of both normal and pregnant Indian ladies, 200·5 mgs per cent and 274.3 mgs per cent respectively, were considerably less than those of American women who showed 300 mgs per cent in the normal state and 440 mg per cent during pregnancy (Ratnoff and Holland, 1959).

The diverse factors that affect fibrinogen level in the blood have been mentioned in earlier communication (Chiplunkar *et al*, 1963). But none of these, specifically tissue damage, aseptic inflammation, injury or infection were observed in the pregnant ladies. The probability of placental tissue with its rich vascular supply being the source of stimulation has to be kept in view since it is known that substances like endogenous polysaccharides released by tissues can cause an elevation of fibrinogen.

Fibrinolytic activity:—In normal state, the fibrinolytic activity, as expressed by the degree of clot lysis, is found to lie between 4 and 10 per cent with only one reading of 2 per cent and shows an average value of 5·84±0·7 per cent. In the second half of pregnancy, there is considerable decrease of fibrinolytic activity, some samples showing negligible action. The average value was 2·6±0 4 per cent. The decrease was statistically significant.

Fibrinolysis is an important physiological function of the mammalian body related to the removal of small fibrin deposits in the vascular system, before they can cause occlusion and infarction. Fibrinolysin or plasmin, not only dissolves fibrin but markedly interferes with thromboplastin generation, prothrombin activation and fibrin formation. The lysin needs other active substances like plasminogen found in the tissues. Many facets in this reaction are still not well understood.

The decrease in the lytic activity observed in the later months of pregnancy does not seem normally to exert any adverse effect in pregnancy and is probably compensated by hyper-fibrinoginaemia and increase of other coagulation factors during this period. Quantitative alterations in these various components would naturally be expected to give rise to clinical disorders.

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