PLASMA FIBRINOGEN AND FIBRINOLYTIC ACTIVITY IN SALINE AND PROSTAGLANDIN INDUCED ABORTION†

by

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Study of coagulation mileu has attained great importance since reports have been published from several centres (Stander *et al*, 1971; Halbert *et al*, 1972; Beller *et al*, 1972; Weiss *et al*, 1972) on the development of coagulation disorder and haemorrhage following intra-amniotic injection of hypertonic saline in an attempt to induce midtrimester abortion. Studies made in various centres showed in general a great decrease in platelet count and fibrinogen level, a significant increase in fibrinogen-fibrin degradation products and an accelerated euglobulin clot lysis time.

Since intraamniotic instillation of hypertonic saline is the most frequently used method for mid-trimester pregnancy termination in our place, the reported dangers of defibrination and haemorrhage have prompted us to study the alterations, if any, in the coagulation mechanism following saline-induced abortions. Few cases of prostaglandin induced abortions have also been studied. We have measured two important parameters of the coagulation system, namely, plasma fibrinogen level and fibrinolytic activity.

Material and Methods

Thirty patients were studied in the Department of Obstetrics & Gynaecology (Eden Hospital), Medical College, Calcutta. Twenty-three patients had 20 percent 200 ml. hypertonic saline injection into the amniotic sac, 3 patients had intraamniotic 200 ml. normal saline instillation and 4 patients had 50 mg PGF_2 alpha injected into the amniotic sac. In both the saline groups, syntocinon drip was started 2 hours after saline injection: 10 units of syntocinon in 540 ml. of 5 percent dextrose solution was given once only.

Plasma fibrinogen was estimated by a chemical test by Biuret method (After R. Richterich) while fibrinolytic activity was measured by euglobulin clot lysis time on the principle enunciated by Buckell (1958).

Blood samples were drawn thrice: just before instillation of the drug (0

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hour), at 2 hours and 24 hours post-instillation interval.

Results

Twenty-three patients had intraamniotic hypertonic saline instillation (I.A.H.S.)—9 were carrying 18 weeks' and 14 were carrying 20 weeks' pregnancy. Of the 3 cases having intraamniotic normal saline instillation I.A.N.S.), 2 were of 18 weeks and 1 was of 20 weeks' gestation and of the 4 cases having intraamniotic prostaglandin F_2 alpha injection (I.A.P.G.), 2 were of 18 weeks and other 2 of 20 weeks gestation. Of these 30 cases, 13 were carrying 18 weeks gestation and the plasma fibrinogen level at 0 hour varied between 300 to 625 mg per cent (average being 485.6 mg per 100 ml.), 17 had 20 weeks pregnancy and the plasma fibrinogen level at 0 hour varied between 350 to 625 mg. per cent (average being 492.1 mg. per 100 ml.). Euglobin Clot Lysis time (E.C.L.T.) values at 0 hour varied between 130 to 155 minutes (average 141 minutes) at 18 weeks and between 110 to 160 minutes (average 144 minutes) at 20 weeks pregnancy.

Table-I shows the plasma fibrinogen level and the (E.C.L.T.) when the abortion time was 12 hours.

TABLE I

Abortion time—12 hours using 20% hypertonic saline

Case No.	Gestational age	Plasma fibrinogen (mg. per cent) 0 hour	2 hours	24 hours	E.C.L.T. (in minutes) 0 hour	2 hours	24 hours
1.	18 weeks	525	700 (33.3)	750 (42.9)	140	160 (14.2)	160 (14.2)
2.	20 weeks	600	625 (4.16)	975 (62.5)	148	140 (-5.4)	160 (8.1)
3.	20 weeks	525	650 (23.8)	680 (29.5)	150	150 (0.0)	165 (10.0)

N.B.:—Figures in parenthesis show percentage increase/decrease compared to basal level at 0 hour.

The Table shows that when the abortion time was 12 hours, there was increase in plasma fibrinogen level to average 15.3 per cent at 2 hours post-instillation sample and 44.9 per cent at 24 hours sample. Corresponding average figures for E.C.L.T. were increases of 2.9 per cent at 2 hours and 10.8 per cent at 24 hours when compared to the basal level at 0 hour. Only in one case (case No. 2) E.C.L.T. was shorter at the 2nd hour and in case No. 3 E.C.L.T. showed no change in the 2nd hour.

Table-II shows the values for fibrinogen and E.C.L.T. when the abortion time was 24 hours.

TABLE II

Abortion Time—24 Hours Using 20% Hypertonic Saline

Case No.	Gestational age	Plasma fibrinogen (mg. per cent)			E.C.L.T. (in minutes)		
		0 hour	2 hours	24 hours	0 hour	2 hours	24 hours
4.	18 weeks	525	650 (23.8)	525 (0.0)	155	180 (16.1)	180 (16.1)
5.	18 weeks	500	575 (15.0)	650 (30.0)	140	150 (7.1)	160 (14.2)
6.	18 weeks	300	375 (25.0)	475 (58.3)	130	140 (7.7)	160 (23.1)
7.	18 weeks	525	650 (23.8)	725 (38.9)	140	135 (—3.7)	140 (0.0)
8.	18 weeks	550	700 (27.2)	925 (68.1)	155	165 (6.4)	170 (9.6)
9.	18 weeks	388	525 (35.3)	480 (23.7)	148	160 (8.1)	180 (21.6)
10.	20 weeks	555	665 (19.8)	500 (—9.9)	140	150 (7.1)	165 (17.8)
11.	20 weeks	625	700 (12.0)	900 (44.0)	135	140 (3.7)	155 (14.8)
12.	20 weeks	600	700 (16.6)	800 (33.3)	135	145 (7.4)	135 (0.0)
13.	20 weeks	400	500 (25.0)	600 (50.0)	160	160 (0.0)	180 (12.5)
14.	20 weeks	425	550 (29.4)	550 (29.4)	155	155 (0.0)	150 (—3.2)

N.B.:—Figures in parenthesis show percentage increase/decrease compared to basal level at 0 hour.

Table-II shows the following average values when the abortion time was 24 hours.

Fibrinogen	:	at 2 hours =	22.9% increase (range 12.0 to 35.3%)
		at 24 hours =	33.2% increase (range —9.9 to 68.1%)
E.C.L.T.	:	at 2 hours =	5.4% increase (range —3.7 to 16.1%)
		at 24 hours =	10% increase (range —3.2 to 23.1%)

Case 10 showed a decreased fibrinogen level at 24 hours sample while it showed no change in case 4. E.C.L.T. showed no

change in 2nd hour sample in cases 13 and 14 but exhibited decrease in case 7. At 24 hours sample, case 14 showed decreased E.C.L.T. while it was same in cases 12 and 7.

Table-III shows the plasma fibrinogen and E.C.L.T. values when the abortion time was 48 hours.

TABLE III

Abortion time—48 hours using 20% hypertonic saline

Case No.	Gestational age	Plasma fibrinogen (mg. per cent) 0 hour	2 hours	24 hours	E.C.L.T. (in minutes) 0 hour	2 hours	24 hours
15.	20 weeks	375	450 (20.0)	600 (60.0)	130	135 (3.9)	165 (26.9)
16.	20 weeks	550	650 (18.2)	775 (40.9)	155	148 (—4.5)	170 (9.7)
17.	20 weeks	525	675 (28.6)	750 (42.9)	150	155 (3.3)	150 (0.0)

N.B.:—Figures in parenthesis show percentage increase/decrease compared to basal level at 0 hour.

Table-III shows the following average values when the abortion time was 48 hours.

Fibrinogen	:	at 2 hours =	22.2% increase (range 18.2 to 28.6%)
		at 24 hours =	47.9% increase (range 40.9 to 60.0%)
E.C.L.T.	:	at 2 hours =	0.9% increase (range —4.5 to 3.9%)
		at 24 hours =	12.2% increase (range 0.0 to 26.9%)

E.C.L.T. showed decreased value in case 16 at 2 hours while it was same in 24 hours in case 17.

Table-IV shows the level of plasma fibrinogen and E.C.L.T. when the abortion time varied between 96 and 192 hours.

TABLE V

Abortion time—24 to 96 hours using normal saline

Case No.	Gestational age	Abortion time (hours)	Plasma fibrinogen (mg. per cent)			E.C.L.T. (in minutes)		
			0 hour	2 hours	24 hours	0 hour	2 hours	24 hours
24.	18 weeks	24	625	700 (12.0)	775 (24.0)	140	150 (7.1)	160 (14.2)
25.	18 weeks	24	600	700 (16.6)	750 (24.9)	135	135 (0.0)	145 (7.4)
26.	20 weeks	96	400	480 (20.0)	625 (56.2)	145	140 (—3.4)	150 (3.4)

N.B.:—Figures in parenthesis show percentage increase/decrease compared to basal level at 0 hour.

Table—V shows the average values as follows:—

Fibrinogen : at 2 hours = 16.2% increase (range 12.0 to 20.0%)
at 24 hours = 35% increase (range 24.0 to 56.2%)

E.C.L.T. : at 2 hours = 1.2% increase (range —3.4 to 7.1)
at 24 hours = 8.3% increase (range —3.4 to 7.1)

E.C.L.T. shows a decrease value at 2nd hour in case 26 while there was no change in case 25.

Table-VI illustrates the plasma fibrinogen and E.C.L.T. values while using intra-amniotically PGF_2 alpha and the abortion time varied between 12 to 27 hours.

TABLE VI

Abortion time—12 to 27 hours using PGF_2 alpha

Case No.	Gestational age	Abortion time (hours)	Plasma fibrinogen (mg. per cent)			E.C.L.T. (in minutes)		
			0 hour	2 hours	24 hours	0 hour	2 hours	24 hours
27.	20 weeks	12	425	500 (17.6)	610 (43.5)	140	130 (—7.1)	150 (7.1)
28.	18 weeks	23	425	525 (23.5)	650 (52.9)	142	147 (3.5)	158 (11.2)
29.	18 weeks	26	400	600 (50.0)	725 (81.2)	135	140 (3.7)	150 (11.1)
30.	20 weeks	27	450	575 (27.7)	700 (55.5)	140	145 (3.5)	155 (10.7)

N.B.:—Figures in parenthesis show percentage increase/decrease compared to basal level at 0 hour.

Table—VI shows the average values as follows:—

Fibrinogen	:	at 2 hours =	29.7% increase (range 17.6 to 50.0%)
		at 24 hours =	58.3% increase (range 43.5 to 81.2%)
E.C.L.T.	:	at 2 hours =	0.9% increase (range 7.1 to 3.7%)
		at 24 hours =	10% increase (range 7.1 to 11.2%)

E.C.L.T. showed a decrease in the 2nd hour in case 27.

All the 23 cases who had I.A.H.S. injection (Tables I, II, III and IV, taken together, plasma fibrinogen and E.C.L.T. values were as follows:

TABLE VII

		Average	Range
Fibrinogen	:		
at 0 hour	=	490 mg per 100 ml.	(300—625 mg.)
at 2 hours	=	596 mg. per 100 ml. (21.6 per cent increase)	(375—750 mg.)
at 24 hours	=	690 mg per 100 ml. (40.8 per cent increase)	(475—975 mg.)
E.C.L.T.	:		
at 0 hour	=	144 minutes	(110—160 min.)
at 2 hours	=	151 minutes (4.8% increase)	(135—180 min.)
at 24 hours	=	160 minutes (10.4% increase)	(135—180 min.)

Table VIII summarises the rate of percentage increase in plasma fibrinogen and E.C.L.T. values at 2nd and 24 hours blood sample when compared to the basal values (0 hour) in the three series having IAHS, IANS and I.A.P.G.

TABLE VIII

		I.A.H.S. series	I.A.N.S. series	I.A.P.G. series
2 hours sample	Fibrinogen	21.6%	16.2%	29.7%
	E.C.L.T.	4.8%	1.2%	0.9%
24 hours sample	Fibrinogen	40.8%	35%	58.3%
	E.C.L.T.	10.4%	8.3%	10%

Table VIII evidently shows that at 2 hours post instillation sample, plasma fibrinogen showed an increase from basal level following I.A.N.S. injection, a further increase following IAHS instillation and the highest increase following I.A.P.G. administration. Similar trend was found in the 24 hours blood sample.

E.C.L.T. value at 2 hours showed highest increase following I.A.H.S. injection and 24 hours sample showed lowest value following I.A.N.S. administration.

Plasma fibrinogen showed an increase at 2 hours sample in all the cases of all the series and so also in the 24 hours sample except in case 10 which showed fibrinogen value below the basal figure.

Euglobulin clot lysis time, though showed, on average, an increase, the trend was not uniform. In as many as 13 cases, E.C.L.T. values were either same as basal figure or showed a decrease in the 2 hours or 24 hours blood.

Comment

Large-scale elective induction of abortions was started in our country only following promulgation of the MTP Act (1971) and its practical implementation since May, 1972. Intra-amniotic injection of hypertonic saline found favour as a method of midtrimester abortion because of its easy availability, effectivity and relative safety.

Apart from Japan where this has been used for a long period following second world war (Wagatsuma, 1965), many centres in the West have been using I.A.H.S. for midtrimester abortion for a long time past. Apart from occasional and rare complications of hypernatraemia, renal failure and shock, it was considered free from serious side-effects and pathophysiological effects of intra-uterine saline instillation was not studied until the beginning of this decade when abnormal haemorrhage in one or two cases of saline-induced abortions raised the suspicion of coagulation disorder. Studies were made amongst others by Stander *et al* (1971), Halbert *et al* (1972), Beller *et al* (1972), Weiss *et al* (1972), Easterling *et al* (1972), Laros *et al* (1973), Brenner *et al* (1973), Glueck *et al* (1973), Bell and Went (1973) and Talbert *et al* (1973) and mainly from the University of North Carolina and few other centres in the United States of America. From small series studied, they have all described a state of defibrinogenation which rarely becomes clinically significant. They noted, amongst other parameters, a decrease in platelet count and fibrinogen concentration and an increase of fibrinolysis break down products which means a shorter euglobulin lysis time.

Normally, pregnancy is accompanied by significant changes in the haemostatic mechanism. There is particularly an increase in the coagulation factors and decrease in fibrinolytic activity—a physiological response to ensure haemostasis at labour.

Hypertonic saline instillation into the amniotic sac causes just the opposite changes as has been claimed in the various series mentioned above. The exact cause for this paradox has not been mentioned as yet. Beller *et al* (1973) have suggested tissue thromboplastin release from the disintegrating placenta as a cause. Brenner *et al* (1973) have suggested that hypertonic saline makes the amniotic sac permeable to liquor amnii which is rich in thromboplastin. Bell *et al* (1973) suggested the necessity of sodium for the changes in the coagulation and fibrinolytic systems as coagulopathy failed to develop when abortion was induced by glucose-instillation or mechanical means (Beller *et al*, 1972).

The coagulation milieu has also been studied following intra-amniotic prostaglandin injection in attempts at mid-trimester abortion. Badraoni *et al* (1973), Phillips *et al* (1974) and Dillon *et al* (1974), from study of small series of cases, found increase in coagulation factors and decrease in fibrinolytic activity while Glueck *et al* (1972), Bell *et al* (1973) and Brenner *et al* (1973) found no significant coagulation changes. The earlier workers explained the increases in coagulation parameters as a "response to a mild inflammatory process produced by PG".

In the present study, increased plasma fibrinogen and increased euglobulin clot lysis time (i.e. decreased fibrinolytic activity) were found in all the 3 series whether intra-amniotic hypertonic saline, normal saline or prostaglandin was administered. Beller *et al* (1972) found no change in plasma fibrinogen following I.A.H.S.-induced abortion in 20% of his patients. With similar drugging, Easterling *et al* (1972) and Glueck *et al* (1973) found no shortening in E.C.L.T. In the line of hypothesis suggested by Owen *et al* (1969) (quoted by Weiss *et al* (1972), it may be said that "the plasma level of any procoagulant depends upon its rate of production relative to its rate of utilisation or destruction". In a coagulation milieu with low-grade intravascular coagulation or fibrinolysis, compensatory mechanisms may increase the rate of production or liberation of the procoagulants. And low-grade intravascular coagulation may be initiated by thromboplastin leak into the maternal circulation from liquor amnii and/or disintegrating foeto-placental unit. As to the cause of increase in clotting indices following I.A.P.G. administration, Phillips *et al* (1974) and Dillon *et al* (1974) have already suggested a mild inflammatory response. The mode of action of I.A.H.S. in initiating the process of abortion is not definitely known. It is presumed that it causes deciduitis which in turn releases prostaglandin. Kundu and Mandal (1976) from Eden Hospital, Calcutta, in histopathological study following I.A.H.S. injection, found evidences of mild deciduitis in 12% of their cases. As such an inflammatory factor may also play some part for the observed changes in saline-abortions.

Whatever may be the physio-pathology behind the changing coagulation parameters, in the present study we have found increased plasma fibrinogen and decreased fibrinolytic activity (increased E.C.L.T.) which is contrary to the observations reported from various centres in the world.

It is a well accepted fact that there is an uniform gradual rise in plasma fibrinogen during pregnancy. But a successful abortion in the midtrimester by any abortificient is preceded by a sudden spurt in fibrinogen level. In fact, this may be of prognostic values in cases of threatened abortion and may prelude any conservative therapy.

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