

Placental Transfer of Intravascular Coagulation between Mother and Fetus

A. J. BISHOP, L. G. ISRAELS, V. CHERNICK, AND E. D. ISRAELS^[122]

Departments of Pediatrics and Medicine, University of Manitoba, and the Clinical Investigation Units of Winnipeg Children's Hospital and Winnipeg General Hospital, Winnipeg, Manitoba, Canada

Extract

Pregnant sheep of 110-140 days' gestation were used to determine the effect of intravascular coagulation in the mother upon her fetus and the effect of intravascular coagulation in the fetus upon its mother. Because fetal lambs can be delivered and left attached to the mothers via the umbilical cord without placental separation, coagulation studies on a mother and her corresponding fetus could be done simultaneously. When intravascular coagulation was induced in the mothers by administering thromboplastin infusions intravenously, the attached fetal lambs also developed intravascular coagulation with decreased levels in platelets, fibrinogen, and factor V, and prolongation of prothrombin, thrombin, and partial thromboplastin times. When intravascular coagulation was induced in fetal lambs, the dam had a drop in platelet count, a minimal drop in fibrinogen levels, and the appearance of fibrin breakdown products in serum and urine.

The factor or factors that crossed the placenta initiating this transfer of coagulation abnormalities are not known. It has been demonstrated that the transfer was not due to fibrin or fibrinogen breakdown products, nor to the infused thromboplastin, and that the trauma of surgery or hypoxia did not contribute to the coagulation abnormalities. The mothers consistently developed fibrin breakdown products in the serum and urine when intravascular coagulation was induced. This was in contrast to the results observed in fetal lambs, which, with one exception, did not show evidence of fibrin breakdown products in serum or urine under identical experimental conditions. These observations suggest the fibrinolytic system of the fetus is inefficient compared with that of the adult; this could be a considerable disadvantage in the presence of intravascular coagulation.

Speculation

As a result of intravascular coagulation in the mother or the fetus a stimulus is produced on the opposite side of the placental barrier resulting in similar changes in the placental partner. This mechanism may be of significance in the etiology of fetal death in eclampsia.

Introduction

Defects in hemostasis have been described in women with toxemia of pregnancy with preeclampsia or eclampsia [28, 45, 54, 68, 74, 75, 94, 99], abruptio

placentae [4, 7, 29, 33, 39, 53, 69, 72, 76, 82, 87, 98, 111], amniotic fluid embolism [53, 68, 83, 86, 88, 99, 102], retention of a dead fetus [36, 53, 67, 68, 70, 71, 73, 89, 99, 109, 113], and sepsis [53, 68, 99]. The pathogenesis of coagulation abnormalities has been

attributed to acute or chronic intravascular coagulation [29, 53, 57, 58, 68, 72, 92, 94, 97, 99, 106, 108]. There is little information, however, regarding necropsy findings in stillborns or the coagulation status of newborns surviving these pregnancies.

That intravascular coagulation occurs in the neonate has only recently been recognized [47], and the concept that intravascular coagulation may occur in the fetus *in utero* is relatively new [19, 61]. It is significant that a number of newborns with intravascular coagulation recognized within 48 hr of birth and stillborns with the pathological findings of disseminated intravascular coagulation are from pregnancies complicated by sepsis, toxemia with preeclampsia or eclampsia [12, 18, 38, 47], partial or complete abruptio placenta [31, 104, 105], or retention of a dead macerated twin [10, 61, 90]. All of these aberrations are known to be associated with intravascular coagulation in the mothers. Information regarding the coagulation status of the mothers of these infants is strikingly absent. This association of coagulation disorders in the mother or fetus associated with disease on the other side of the placenta strongly suggests that the stimulus is capable of crossing the placenta. However, as simultaneous studies of the coagulation system are difficult to obtain in mother and fetus under these clinical circumstances, an animal system was used to study the effects of intravascular coagulation induced in the mother or fetus on its placental partner.

Since a lamb may be delivered and left attached to its mother via the umbilical cord without placental separation for many hours, pregnant sheep of 110–140 days' gestation were used to determine the effect of intravascular coagulation in the mother upon her fetus, and the effect of intravascular coagulation in the fetus upon its mother.

Materials and Methods

Fibrinogen

Adult sheep fibrinogen was prepared from citrated plasma (1 part 3.8% sodium citrate to 9 parts blood) by the ethanol fractionation method of Blomback and Blomback [15] followed by glycine extraction and tannic acid precipitation as described by Barnhart and Forman [9]. This procedure yielded fibrinogen at a concentration of 1400–1800 mg/100 ml containing 90–92% clottable protein. Total protein and the clottable fractions were determined by the method of Blomback [14]. Fetal fibrinogen was prepared by the glycine precipitation method of Kazal [44], which yielded fibrinogen preparations at concentrations of 350–600 mg/100 ml with 100% clottable protein.

Fibrinogen Breakdown Products

Breakdown products were prepared from adult fibrinogen by streptokinase digestion [100]. Human euglobulin was added to the system as a source of "proactivator." The digestion was continued for 18–24 hr. On immunoelectrophoresis these "late products" of fibrinogen digestion showed only two lines with α and β mobilities designated, respectively, as E and D by Nussenzweig *et al.* [64]. Fetal and adult D and E were purified as previously described [85]. Fibrinogen breakdown products in the serum and urine were identified immunologically by Ouchterlony gel diffusion [115] using adult and fetal antifibrinogen, anti-D, and anti-E. Serum for fibrin breakdown products was collected in tubes containing thrombin and ϵ -aminocaproic acid (EACA), and urine was collected in bottles containing EACA as previously described [41].

Specific Antisera

Antisera to both adult and fetal fibrinogen, D and E breakdown products were prepared as described previously [85].

Coagulation Tests and Factor Assays

Blood was collected into tubes containing acid citrate and EACA [85]. For plasminogen assays, blood collected without EACA was used. The thrombin time (1 unit/ml) was determined by the method of Fletcher [34] and the partial thromboplastin time by a modification of the method of Proctor and Rapaport [77] substituting celite for kaolin. One-stage prothrombin time and factor V assays were determined by the methods of Quick [78, 79]. The ewes' control samples were considered 100% for factor V. Plasma fibrinogen was assayed by the modification [6] of the method described by Ratnoff and Menzie [81], and plasminogen by the method of Alkjaersig and associates [2].

Animal System

Surgery. Anesthesia was induced in the ewe with Nembutal, 20–30 mg/kg administered intravenously, and light anesthesia was maintained throughout the experiments with intermittent injections of 75–150 mg Nembutal. Fetal lambs were delivered by cesarean section, and umbilical cords were left attached. The lambs were not allowed to breathe air, their heads being immersed in warm isotonic saline. Catheters were inserted into the jugular or femoral vein and the carotid or femoral artery of the fetus, and in the jugular vein and carotid artery of the ewe. The catheters were kept patent with an 0.85% NaCl solu-

tion. All infusions were given intravenously, and the blood was collected for coagulation studies by arterial sampling. Adult and fetal samples were collected simultaneously.

Infusions

Thromboplastin. Intravascular coagulation was induced with thromboplastin infusions (8–12 ml/kg, ewe; 10–15 ml/kg, fetus) given over a period of 10–15 min. Thromboplastin was prepared from fresh human brain [13] suspended in saline. The saline suspensions gave a prothrombin time of 11.5–14 sec.

Heparin. Heparin (175 mg/kg) was administered intravenously to the ewes and heparinization maintained by continuous infusion of 50 mg/kg heparin in 300 ml of 0.85% NaCl solution at the rate of 50–100 ml/hr. Fetal lambs were given 300 mg/kg heparin intravenously and heparinization maintained with a continuous infusion of 300 mg/kg heparin in 150 ml of 0.85% NaCl solution at the rate of 5–10 ml/hr.

Fibrinogen breakdown products. The late products of fibrinogen degradation obtained from 300 mg purified adult fibrinogen suspended in 100 ml saline were infused into the mothers. Breakdown products from 150–300 mg adult fibrinogen suspended in 25–35 ml saline were infused into the fetal lambs.

Experimental. The animals were divided into the following groups. *Group I:* Thromboplastin infusions (11): A. thromboplastin infused into the mother (6); B. thromboplastin infused into the fetus (3); C. thromboplastin infused into a 2- and a 7-week-old lamb (2). *Group II:* Heparin plus thromboplastin (2). These animals were heparinized as described. When the partial thromboplastin time was prolonged to 2 min and the whole blood clotting time was in excess of 30 min, the thromboplastin infusion was started. A. Heparin followed by thromboplastin into mother; B. heparin followed by thromboplastin into fetus. *Group III:* Infusions of late products of fibrinogen degradation products (5): A. fibrinogen breakdown products infused into the mother (2); B. fibrinogen breakdown products infused into the fetus (3). *Group IV:* Animals subjected to identical anesthesia and surgical methods as those in *groups I, II, and III* but not infused (3).

Results

Comparison of Coagulation Tests and Factor Levels in Ewes and Their Fetal Lambs

Table I compares the prothrombin, partial thromboplastin and thrombin times, plasminogen, fibrinogen, factor V levels, and platelet counts of each mother

and her corresponding fetus. These are control samples taken prior to any infusion.

The prothrombin and partial thromboplastin times of the fetal lambs were invariably longer than those of their dams. This was also true for the thrombin times in most animals. The fibrinogen, plasminogen, and factor V assays were lower in the fetus. These findings are in agreement with values reported in human newborns [1, 3, 26, 35, 42, 51, 63].

There was a wide variation in platelet counts in both the mother and fetus, but platelet counts in fetal blood did not differ significantly from maternal values. The fetal lambs had gestational ages of 110–140 days; however, the numbers were insufficient to compare fetal values at different gestational ages.

Thromboplastin Infusion (Group I)

Thromboplastin infusion into the mother. As seen in Figure 1, when thromboplastin was infused into the mother, intravascular coagulation was quickly induced, as evidenced by the rapid decrease in platelets, marked increase in partial thromboplastin, thrombin, and prothrombin times. Fibrinogen levels decreased from 340 to 15 mg/100 ml. Factor V levels also decreased from 100 to 20%. Fibrin breakdown products were present in both the urine and serum of postinfusion samples.

Figure 2 illustrates the coagulation studies in the fetus of the mother shown in Figure 1. Within 25 min of starting the infusion into the mother, there was a drop in the fetal platelet count. The thrombocytopenia became most marked 45 min postinfusion. Two hours postinfusion, the partial thromboplastin and thrombin times were prolonged, and there was a drop in fibrinogen levels. The coagulation abnormalities were most marked 3 hr postinfusion, and at this time the prothrombin time was also prolonged. The factor V level fell from 40% to less than 10%. Fibrin breakdown products were not detectable in the lamb's serum or urine using both fetal and adult antifibrinogen, anti-D, and anti-E. Fragmentation of red blood cells was present in the postinfusion peripheral blood smears of both mother and fetus [25, 91]. There was no significant change in hematocrit between preinfusion samples and the final samples withdrawn in each experiment. Six such experiments were performed with similar findings. Results of the other five experiments are given in Table II.

Thromboplastin infusion into fetus. There were three experiments in which the fetus was infused with thromboplastin. The results are given in Table III and Figures 3 and 4. Figure 3 is an example of a twin

Table I. Comparison of fetal and maternal control samples

	PT ¹		PTT ¹ sec		TT ¹		Factor V, ² %		Fibrinogen, mg/100 ml		Plasminogen, casein units/ml		Platelets/mm ³ ($\times 10^3$)	
	M ³	F	M	F	M	F	M	F	M	F	M	F	M	F
	15	23	29	49	35	42	100	48	512	118			800	565
	14	22	16	22	29	37	100	40	348	129		0.52	482	570
	13	27	24	33	32	40	100	72	509	115		0.07	607	504
	14	24	21	28	28	44	100	30	424	112	2.3	0.84	371	420
	13	16	18	45	28	36	100	80	544	202		0.9	168	561
	13	22	21	30	31	43	100	72	488	78		0.62	363	400
	15	22	33	58	32	37	100	64	533	117		0.62	444	335
	12	19	33	48	30	31	100	54	842	140		0.93	520	360
	13	21	16	30	37	54	100	58	267	107	1.5	1.0	718	470
	16	21	16	36	34	35	100	56	263	157	1.9	0.7	452	576
	12	20	28	44	23	26	100	39	379	199	2.5	0.8	1,094	580
	14	20	29	39	29	28	100	62	379	157	2.9	0.6	291	595
	12	26	20	35	25	34	100	80	368	135	2.3	0.6	612	532
	13	19	40	45	30	33	100	100	320	152	1.8	0.5	624	481
	12	18	34	41	27	29	100	100	528	216	2.7	1.0	381	610
	14	21	25	41	24	32	100	78	331	157	1.7	0.82	467	564
	14	21	24	34	25	29	100	64	623	129	2.9	0.7	622	487
Mean	13.5	21	25	39	29	36		65	450	142	2.3	0.70	530	506

¹ PT = prothrombin time; PTT = partial thromboplastin time; TT = thrombin time.
² The ewes' control sample in each experiment was considered as 100%.
³ M: mother; F: fetus.

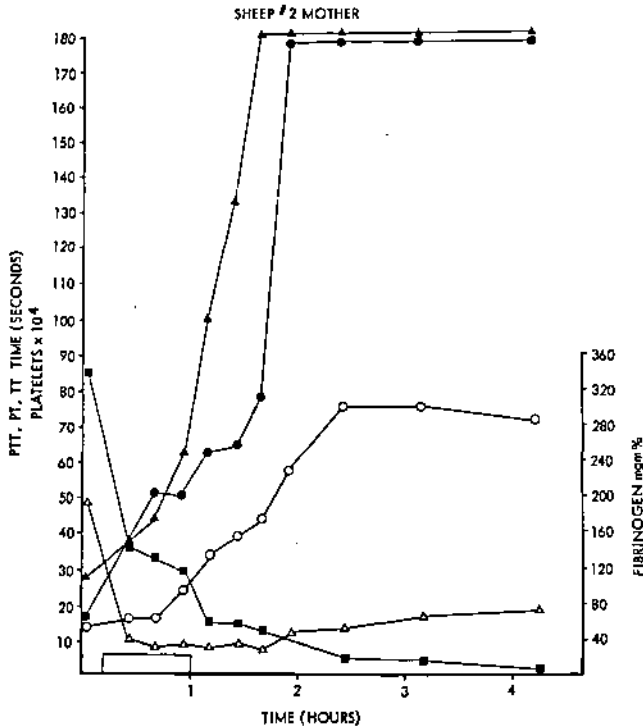


Fig. 1. Mother was infused with thromboplastin, 12 ml/kg, for 50 min (bar). ●: Partial thromboplastin time. ▲: Thrombin time. ■: Fibrinogen. ○: Prothrombin time. △: Platelets.

preparation. *Fetus A* was delivered in the usual manner, and *fetus B* was left *in utero*. Thromboplastin was infused into *fetus A*, and intravascular coagulation was induced as reflected by a decrease in the platelet count and fibrinogen level and an increase in prothrombin, partial thromboplastin, and thrombin times.

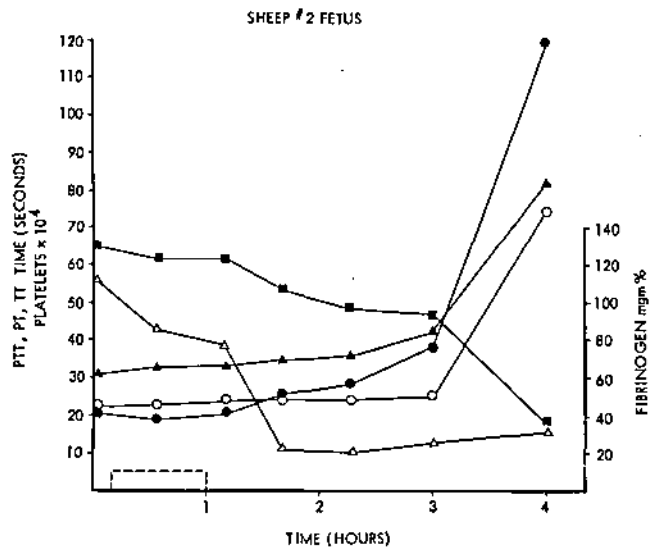


Fig. 2. Fetus of the mother in Figure 1. The bar indicates the thromboplastin infusion into the mother. Symbols as in Figure 1.

Table II. Mother infused with thromboplastin; Simultaneous coagulation studies in fetus and mother¹

Exp. no.	PT		PTT sec		TT		Fibrinogen, mg/100 ml		Platelets/mm ³ (× 10 ⁹)		Factor V, %		Serum		FBP		Urine	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M-1	15	18	29	47	34	39	512	334	800	83	100	54	—	+	—	—	—	+
F-1	22	34	49	67	41	50	118	81	575	209	48	28	—	—	—	—	—	—
M-2	14	72	16	180	29	180	348	16	482	78	100	19	—	+	—	—	—	+
F-2	22	75	21	120	32	86	129	33	570	102	40	6	—	—	—	—	—	—
M-3	13	14	17	28	27	37	544	258	168	40	100	100	—	+	—	—	—	+
F-3	16	22	32	45	35	47	202	78	561	70	80	44	—	—	—	—	—	—
M-4	14	17	21	39	28	44	424	278	371	84	100	40	—	+	—	—	—	+
F-4	24	26	28	42	44	62	112	78	420	73	30	20	—	—	—	—	—	—
M-5	13	15	21	32	31	34	488	308	363	264	100	80	—	+	—	—	—	+
F-5	22	52	30	210	43	183	112	28	400	231	72	24	—	—	—	—	—	—
M-6	13	34	17	32	25	39	612	168	638	246	100	48	—	+	—	—	—	+
F-6	21	47	32	68	35	77	129	58	478	26	48	20	—	—	—	—	—	—

¹ F: fetus; M: mother; PT: prothrombin time; PTT: partial thromboplastin time; TT: thrombin time; FBP: fibrin breakdown products; Pre: preinfusion control sample; Post: maximal change in postinfusion samples; M-1 and M-3 to 6: 8 ml/kg thromboplastin over 50 min; M-2: 12 ml/kg thromboplastin over 50 min.

Table III. Thromboplastin infused into fetus; Simultaneous coagulation studies in mother and fetus¹

Exp. no.	PT		PTT sec		TT		Fibrinogen, mg/100 ml		Platelets/mm ³ (× 10 ⁹)		Factor V, %		Serum		FBP		Urine	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F-10	19	34	48	77	31	40	219	140	360	120	54	21	—	—	—	—	—	—
M-10	12	12	33	32	30	31	842	589	520	414	100	100	—	+	—	—	—	+
F-11	22	49	55	180	32	67	117	55	335	182	44	3	—	—	—	—	—	—
M-11	15	15	33	33	32	32	533	488	488	368	100	100	—	+	—	—	—	+
F-13a	20	43	44	146	25	35	199	124	580	212	42	11	—	+	—	—	—	+
b	20		44		25		180		600	74	48		—	—	—	—	—	—
M-13	12	14	28	30	23	25	380	284	1,094	476	100	100	—	+	—	—	—	+

¹ Abbreviations as in Table II. F-10: 10 ml/kg over 20 min; F-11, 13a, 13b: 15 ml/kg over 5-10 min.

Factor V decreased from 40 to 10%. *Fetus A* was killed after 1.5 hr, and *fetus B* was delivered. *Fetus B* was then infused with thromboplastin. It will be noted that the preinfusion values of platelets, fibrinogen, prothrombin, partial thromboplastin, and thrombin times were similar to the control values for *fetus A*.

Figure 4 gives the results in the mother of the twins shown in Figure 3. Within 5 min of completing the thromboplastin infusion into *fetus A*, there was a decrease in the mother's platelet count. Over the next 2 hr, no further decrease in platelet count occurred; other coagulation tests and factor levels remained essentially normal. Fifteen minutes after the infusion into *fetus B* was complete, there was a further fall in the mother's platelet count and her fibrinogen level decreased from 380 to 284 mg/100 ml. Fibrin breakdown products appeared in the mother's serum 5 min after the thromboplastin infusion into *fetus A* was completed and were present throughout the remainder

of the experiment. Fibrin breakdown products were also found in the mother's urine.

Of the four fetal lambs infused with thromboplastin, in only one (*twin A*, Fig. 3) could fibrin breakdown products be identified in the serum or urine (Table III).

Thromboplastin infusion into the newborn. When thromboplastin was infused into a 2-week-old lamb (Fig. 5), intravascular coagulation was induced but fibrin breakdown products did not appear in the serum or urine. Similar results were obtained when thromboplastin was infused into a 7-week-old lamb.

Heparin and Thromboplastin Infusions (Group II)

Heparin and thromboplastin infusions into the mother. With the heparin regimen previously described, the mother's partial thromboplastin time was prolonged beyond 2 min, and the whole blood clotting time was in excess of 30 min. The partial thrombo-

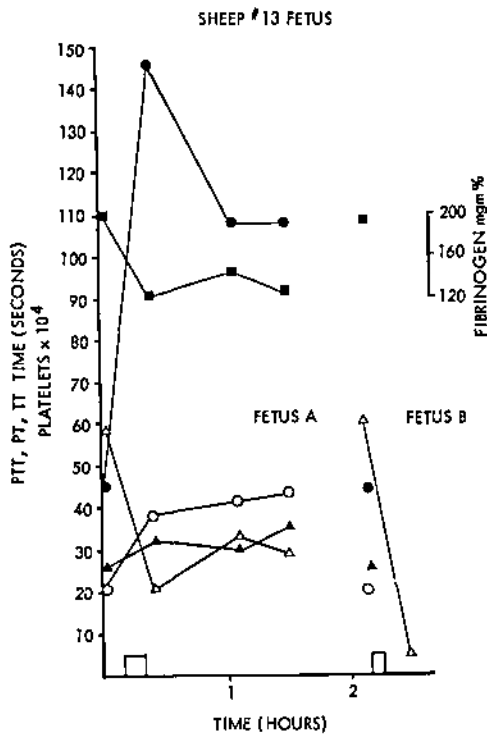


Fig. 3. Twin preparation; bars indicate the thromboplastin infusions into the fetal lambs (fetus A, 15 ml/kg over a 10-min period; fetus B, 15 ml/kg over a 5-min period). Symbols as in Figure 1.

plastin time and whole blood clotting time of her fetus, however, were unchanged. When the heparinized mother was infused with thromboplastin, intravascular coagulation was not induced, and the coagulation tests and factor levels in her fetus remained normal.

Heparin and thromboplastin infusions in the fetus. When the fetus was heparinized, its partial thromboplastin time was prolonged beyond 2 min and its whole blood clotting time was longer than 1 hr. The mother's partial thromboplastin and whole blood clotting times remained unchanged. When the heparinized fetus was infused with thromboplastin, it did not develop intravascular coagulation, and the coagulation tests and factor levels of the attached mother were unchanged.

Infusion of Late Products of Fibrinogen Degradation (Group III)

Fibrinogen breakdown products infused into the mother. When the late products of fibrinogen digestion were infused into the mother, platelet counts, factor V, and fibrinogen levels did not fall and partial thromboplastin, thrombin, and prothrombin times remained

normal. The coagulation tests and factor levels in the attached fetal lambs remained unchanged. Fibrin breakdown products were identified in the serum and urine of the mothers but were not present in either the serum or the urine of their fetal lambs.

Fibrinogen breakdown products infused into the fetus. When the late products of fibrinogen degradation were infused into the fetus (Fig. 6), there was a marked decrease in the platelet count but only minimal changes in the coagulation tests. Factor V levels did not decrease. The coagulation status of the mother remained normal. Fibrin breakdown products were present in both the serum and urine of the infused fetus but were not present in either the serum or urine of the mother. Table IV summarizes the findings in the other two animals of this group.

Anesthesia and Surgery without Infusions (Group IV)

These animals had anesthesia and surgery identical with the experimental groups and the same amounts of blood were withdrawn for coagulation studies. Fibrin breakdown products did not appear in the serum or urine and the partial thromboplastin, prothrombin, and thrombin times remained normal; this applied to both fetus and mother. One animal was made intermittently anoxic by breathing nitrogen so that arterial PO_2 decreased from 120 to 20 mm for 5-min periods without producing any abnormality in the coagulation

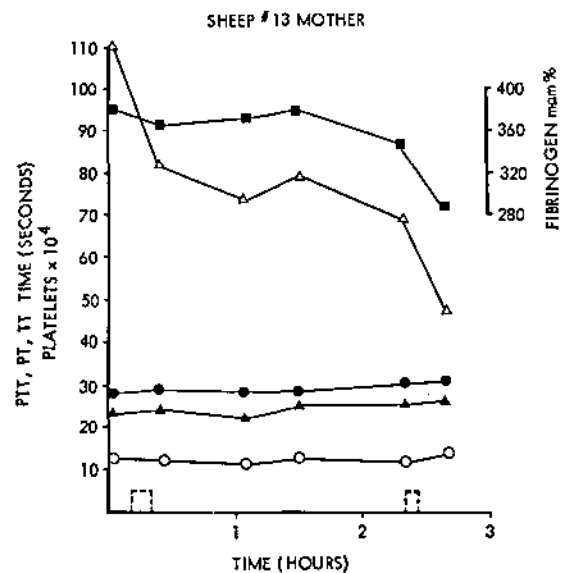


Fig. 4. Mother of the twins shown in Figure 3. The bars indicate the thromboplastin infusions into the fetal lambs. Symbols as in Figure 1.

status of the mother or fetus. One fetus was rendered anoxic via intermittent cord clamping, but neither fetus nor mother developed any coagulation abnormalities.

Discussion

It has been postulated by Schneider [92, 95, 96] and others [53, 65, 76,] that the bleeding diathesis seen in parturient women with abruptio placenta is initiated by massive infusion of decidual thromboplastin into

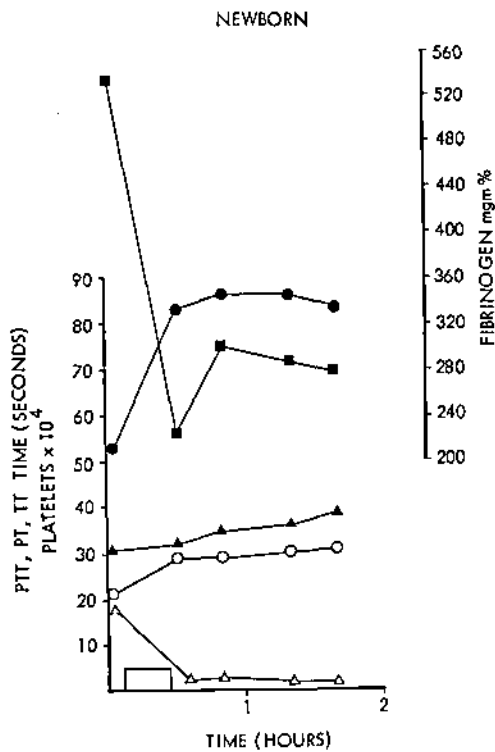


Fig. 5. Thromboplastin infused into a 2-week-old lamb (10 ml/kg over a 25-min period) as indicated by the bar. Symbols as in Figure 1.

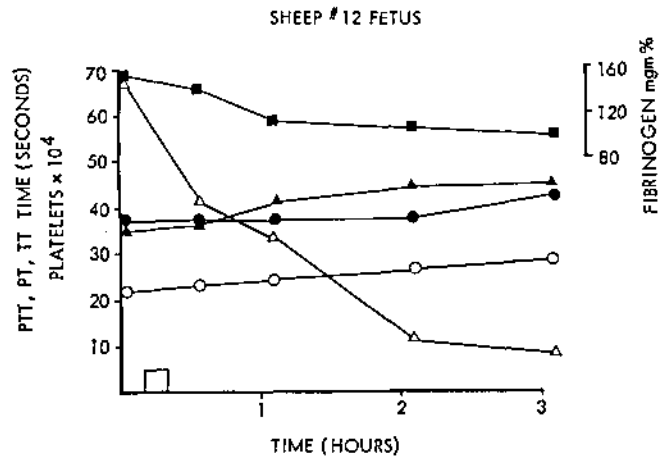


Fig. 6. Bar indicates fibrinogen breakdown products infused into the fetus. Symbols as in Figure 1.

the mother's circulation from rupture of the decidual plate at the time of placental separation. The possibility of this agent entering the fetal circulation, however, was not mentioned. Intravascular coagulation and the generalized Shwartzman reaction may also be produced in animals by trauma to the placenta [24, 93], and intravascular coagulation has been reported in a rabbit following spontaneous premature separation of the placenta [5]. Although there are numerous reports in the literature of coagulation abnormalities in women with abruptio placenta, little mention is made of the coagulation status of the infants who survived this complication or the pathological findings in stillborns.

Similarly, intravascular coagulation following amniotic fluid embolism is well documented [68, 84, 99], but, again, information concerning the fetus is lacking. In this situation, the thromboplastic substance responsible for the coagulation abnormalities is thought to be the debris and particulate matter of the amniotic fluid since amniotic fluid free of this material is not thromboplastic [107, 112]. In pregnancies complicated

Table IV. Fetal lambs infused with fibrinogen breakdown products: Simultaneous coagulation studies in fetus and mother¹

Exp. no.	PT		PTT sec		TT		Fibrinogen, mg/100 ml		Platelets/mm ³ (× 10 ⁴)		Factor V, %		Serum FBP		Urine	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F-7	20	25	38	52	28	37	157	112	593	121	62	60	-	+	-	+
M-7	13	12	29	29	30	32	379	370	291	266	100	100	-	-	-	-
F-8	21	31	30	49	54	62	106	89	470	40	58	44	-	+	-	+
M-8	13	13	16	19	37	35	267	298	718	686	100	100	-	-	-	-
F-12	21	28	37	43	35	44	157	101	676	108	56	42	-	+	-	+
M-12	16	16	16	20	33	32	292	314	452	514	100	100	-	-	-	-

¹ Abbreviations as in Table II.

by prolonged retention of a dead fetus, the intravascular coagulation may be initiated by thromboplastic material from the placenta, macerated fetus, or amniotic fluid, and the coagulation abnormalities may be mild or severe [68]. The coagulation abnormalities in patients with toxemia, or with preeclampsia or with eclampsia have also been related to the generalized Shwartzman reaction and intravascular coagulation [53, 57].

In animal experiments a high rate of abortion and fetal death occurred when intravascular coagulation was induced in the mother with endotoxin [53, 56, 58, 116], progesterone [53, 103], or abnormal lipid diets [53, 55, 62, 114], and the placental changes seen in the animals were similar to those seen in human toxemias. McKay *et al.* [53] suggested that the process begins with changes in the trophoblast leading to focal thrombosis and infarction of maternal vascular channels. Trophoblastic damage increases with leakage of clot-promoting factors from the placenta producing thrombosis of decidual and uterine veins. The resultant congestion of the placenta may lead to bleeding into the decidua and uterine cavity, premature separation of the placenta, and fetal death, providing further thromboplastic material.

The infants of such complicated pregnancies may also develop coagulation abnormalities. Boyd (19-23) has described disseminated fibrin thromboembolism in stillborns, many of whom were from pregnancies complicated by toxemia, preeclampsia and eclampsia, and premature separation of the placenta. Coagulation studies were not available on these mothers. It was suggested that placental thromboplastin may be capable of entering the fetal circulation to cause a syndrome in the fetus similar to that found in maternal hypofibrinogenemia [21, 22]. Other reports of coagulation abnormalities or intravascular coagulation in the newborn from pregnancies complicated by toxemia, abruptio placenta, or amniotic fluid embolism have been made by Edson [31], Hathaway [38], Kennan (*case 4*) [45], Leissring [47], Valentine [105], Bloom [16], Bolen [18], and Stark [104].

Newborns with bilateral renal cortical necrosis and other findings associated with intravascular coagulation have been described by Moore [61], Reisman [90], and Bernirschke [10] all in association with a dead macerated twin. Bernirschke [10] postulated that fetofetal exchange of thromboplastic material from the dead fetus through vascular shunts in a monochorionic placenta was responsible for this syndrome. Bernstein [12] reported 11 cases of renal cortical necrosis in new-

borns of mothers with preeclampsia, eclampsia, placenta previa, and uterine or uteroplacental hemorrhage.

In the present study, with pregnant sheep, it is evident that coagulation abnormalities in the mother were accompanied by similar changes in her fetus and coagulation abnormalities in the fetus affected the coagulation status of the mother. The induction of intravascular coagulation in pregnant ewes was rapidly followed by intravascular coagulation in the fetal lambs with a rapid drop in platelet count, prolongation of prothrombin, thrombin, and partial thromboplastin times, and a decrease in fibrinogen and factor V levels. When intravascular coagulation was induced in the fetus, the mother showed a drop in platelet count and a minimal decrease in fibrinogen levels with minor changes in prothrombin, partial thromboplastin, or thrombin times. Animals undergoing the same anesthesia and surgical procedure with or without induced anoxia did not develop any of the coagulation abnormalities described in the fetus or the mother.

That the transfer of the coagulation abnormalities is not due to the infused thromboplastin crossing the placenta can be demonstrated by heparinization of the thromboplastin recipient. Since heparin does not cross the placental barrier [37], it is possible to anticoagulate either the mother or the fetus. If the infused thromboplastin crosses the placental barrier, the fetus of a heparinized thromboplastin-infused mother should develop evidence of intravascular coagulation. In such an experiment, however, the coagulation status of the fetus remained unchanged. Similarly, the mother of a heparinized thromboplastin-infused fetus did not develop any coagulation abnormalities. These experiments indicate that the transfer of the coagulation defect to the placental partner of a thromboplastin-infused mother or fetus is not the result of the infused thromboplastin crossing the placental barrier but requires active intravascular coagulation in the fetus or mother or at least on their corresponding sides of the placental vasculature.

The precise role played by the placenta is not known. In our animals there were no gross infarcts, hemorrhage, or separation of the placenta. Microscopic evaluation must await normal control studies of sheep placentas at varying gestational ages, especially in regard to trophoblastic degeneration and fibrin deposition. This information is available for human placentas [60].

It was also demonstrated that fibrinogen breakdown products do not cross the placental barrier. As shown

in Table V, when the late products of fibrinogen degradation were infused into the mother or the fetus, they were not detectable in the serum or urine of the noninfused placental partner, nor did the latter develop any coagulation abnormalities. Although fibrinogen breakdown products are not the responsible factor for the placental transfer of intravascular coagulation, the response of the fetal or adult recipient to the infused breakdown products was different. The thrombocytopenia induced in the fetus infused with late fibrinogen breakdown products was probably due to the platelet-aggregating effect of product D, as shown by Barnhart [8]. The slight decrease in fibrinogen and mild prolongation of thrombin, prothrombin, and partial thromboplastin times could also be a direct result of the infused late products of fibrinogen degradation which are capable of forming soluble complexes that interfere with the conversion of fibrinogen to fibrin by thrombin [46, 49, 59]. It is also possible that during platelet aggregation some platelet changes occurred, releasing platelet factors 3 or 4 [48] and thereby inducing mild intravascular coagulation in the fetus which was not severe enough to affect the mother's coagulation system. When the late products of fibrinogen degradation were infused into the mothers, there were no significant changes in their platelets or other aspects of their clotting system, nor were there any coagulation abnormalities in the attached fetal lambs. The difference in the response of the fetus and the adult to infusion of breakdown products may be related to the much higher dose per kilogram given to the fetal lambs.

It is of interest that fibrin breakdown products formed *in vivo* in the mother as a consequence of direct thromboplastin infusion or indirectly by thromboplastin infusion into the fetus also do not cross the placental barrier (Table V). It has been shown, with one exception, that the fetal lambs with intravascular coagulation, whether induced by direct thromboplastin infusion or thromboplastin infusion into the mothers, do not show fibrin breakdown products in either the serum or urine although the fetus is capable of renal clearance of these products. The fetus is not forming late breakdown products and clearing them via the placenta into the mother since the fibrinogen breakdown products do not cross the placental barrier. This is in contrast to the mothers, who invariably have fibrin breakdown products in both the serum and the urine under the same experimental conditions. These observations suggest that the fibrinolytic system of the fetus is inefficient compared with that of the adult. Similarly,

Table V. Appearance of fibrin breakdown products under different experimental conditions

Infusion	Mother		Fetus	
	Serum	Urine	Serum	Urine
A. Thromboplastin				
Into mother	6/6 ¹	6/6 ¹	0/6 ¹	0/6 ¹
Into fetus	3/3	3/3	1/4	1/4
B. Thromboplastin plus heparin				
Into mother	0/2	0/2	0/2	0/2
Into fetus	0/2	0/2	0/2	0/2
C. Breakdown products				
Into mother	3/3	3/3	0/3	0/3
Into fetus	0/4	0/4	4/4	4/4

¹ Results are ratios of the number of animals showing breakdown products to the number of animals in each experimental group.

lambs up to 7 weeks of age also did not develop fibrin breakdown products in serum or urine following thromboplastin infusion.

The reasons for this difference between the adult and fetal fibrinolytic systems are not known. The ratio of plasminogen to fibrinogen is not consistently lower in the fetus than in the adult, although absolute values of both fibrinogen and plasminogen are lower. When intravascular coagulation is induced in the fetus, the plasminogen level does decrease (Table VI). It is not known whether the plasminogen is being activated and converted to plasmin but is present in insufficient quantity to lyse the fibrinogen or fibrin formed, or if the plasminogen is not activated but simply decreased because of adsorption onto the fibrin [101]. The ratio of inhibitor to activator in the fetus is also not known. That the lytic system of human newborns is different from that of adults was first suggested by Boisvert [17]. He observed that blood clots from newborn infants, in contrast to those of their mothers, were resistant to lysis in the presence of streptococcal culture supernates. He

Table VI. Fetal lambs with intravascular coagulation: Comparison of pre- and postinfusion fibrinogen and plasminogen levels

Exp. no.	Fibrinogen, mg/100 ml		Plasminogen, casein units/ml	
	Pre	Post	Pre	Post
F-2	129	33	0.6	0.2
F-3	202	78	0.9	0.7
F-4	112	78	0.8	0.3
F-5	112	28	0.8	0.3
F-6	129	58	0.6	0.1
F-11	117	55	0.6	0.0
F-13a	199	124	1.1	0.8

postulated the existence of a nonspecific inhibitor of fibrinolysis in the newborn. Since that time the reports on the lytic system of the newborn have been conflicting. Some [11, 27, 30, 32, 43] reported increased fibrinolytic activity of cord blood; others [66, 80] reported decreased fibrinolytic activity. Boyd [19] also suggested decreased lytic activity of the fetus, and Zilliacus [117] stated that the lytic activity decreases with aging of the fetus. Some of the studies showing increased fibrinolytic activity in the newborns may well have been measuring fibrinolysis *in vitro*, unless the samples were collected in inhibitors of fibrinolysis such as bovine protease inhibitor [118] or ϵ -aminocaproic acid [101]. This is particularly important when umbilical cord blood samples are used, since tissue activator of the fibrinolytic system may easily contaminate such specimens.

Summary

In pregnancies complicated by abruptio placenta, amniotic fluid embolism, toxemia with preeclampsia or eclampsia, and retention of a dead fetus, hemostatic defects due to intravascular coagulation may occur. There is indirect evidence that the infants of such pregnancies may also develop coagulation abnormalities. In the present study, using pregnant sheep as the animal model, intravascular coagulation was induced with thromboplastin infusions into the mother or the fetus, and both were studied simultaneously. These experiments have shown that acquired coagulation abnormalities can be transferred from the mother to her fetus and from the fetus to its mother. This transfer is not due to the infused thromboplastin nor fibrin breakdown products crossing the placental barrier but requires active intravascular coagulation in the recipient or the recipient's side of the placental vasculature. It is also suggested that the fibrinolytic system of the fetus is inefficient compared with that of the adult.

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119. We wish to express our thanks to Mrs. L. Baxter, Miss L. Bangard, Miss J. Routly, and Mr. B. Russell for technical assistance, and to Dr. F. Wong for assistance with surgical preparations.
120. Dr. A. J. Bishop, Centennial Fellow, Medical Research Council of Canada.
121. Supported by grants from the Manitoba Heart Foundation and the Medical Research Council of Canada.
122. Requests for reprints should be addressed to: E. D. Israels, M.D., Manitoba Institute of Cell Biology, 700 Bannatyne Avenue, Winnipeg 3, Manitoba, Canada.
123. Accepted for publication April 23, 1970.